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THE JOURNAL OF
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CHRONIC PROGRESSIVE OPHTHALMOPLEGIA OF MYOPATHIC ORIGIN

BY

P. H. SANDIFER

(RECEIVED 23RD JULY, 1946)

THE term "chronic progressive ophthalmoplegia" signifies a syndrome characterized by a slowly progressive weakness of the external ocular muscles. In the past the term has been applied loosely, for cases have been called chronic progressive ophthalmoplegia which differ from each other in important respects. Thus, in some instances the paralysis has been confined to the levators of the upper lids (Fuchs, 1890, and Collins, 1909); in others complete external ophthalmoplegia has been present, notably in the cases of Beaumont (1900), McMullen (1912), Altland (1909), McMullen and Hine (1921). Usually the intrinsic eye muscles escape, but this is not always the case. Sometimes there has been associated weakness of the orbicularis oculi (Beaumont, 1900) and of other muscles of the face and of the limbs (McMullen and Hine 1921). In some there has been no family history, whilst in others the disease has been hereditary (Ayres, 1896; Cooper, 1910; Bradburne, 1912; Crouzon, 1929). The scanty pathological material has shown that the oculo-motor nuclei may be the site of degenerative changes in some instances but not in others. In 1900 Wildbrand and Saenger grouped together certain cases of external ophthalmoplegia because they believed them to have characteristics which separated them from a congenital type on the one hand and a type symptomatic of neurological disease extending beyond the oculo-motor territory on the other. This group, which they separated, they believed formed a clinical entity which had the following characteristics: the onset was usually in infancy or early childhood; the progress was very slow, extending over periods as long as 30 or 40 years; ptosis was usually the first sign, to be followed by increasing restrictions of the external ocular movements, typically without diplopia; the paralysis might halt for long periods, but as a rule complete fixation of the eyeballs was the final state, though the ptosis was seldom complete. The pathology underlying the symptoms of this group still remains a problem. Nuclear degenerative changes have been thought to be the cause of the paralysis, but in the absence of conclusive proof, notably by Cooper (1910) and Crigler (1914). The term "chronic progressive nuclear ophthalmoplegia" has been applied to those cases showing a slowly increasing oculo-motor palsy which is presumed to be due to degeneration of the cells of the 3rd, 4th, and 6th cranial nerve nuclei. The few published accounts of this condition have been reviewed by Wildbrand and Saenger (1900): in some of the cases studied degenerative changes have been found in the oculo-motor nuclei; but even so it has been impossible to determine if the degeneration has been primary, or secondary, to some other disease process.

The syndrome of gradually increasing oculo-motor paralysis may certainly be produced in several ways. It may be the first sign of disease involving muscles or neuro-muscular junctions, as may be the case in myotonia atrophica, progressive spinal muscular atrophy (Werdnig-Hoffman's disease), and myasthenia gravis. It may be an early manifestation of such conditions as Parkinsonism, tabes dorsalis, or syringobulbia. To avoid confusion, care should be taken in signifying the groups which Wildbrand and Saenger have distinguished. Where the syndrome is symptomatic and is witnessed in a setting of some well-recognized disease the symptoms of which extend beyond the oculo-motor muscles, the term "chronic progressive ophthalmoplegia" should not be used unless qualified by the name of the disease of which it forms a part. Classification of cases of chronic progressive ophthalmoplegia is not a mere academic exercise but a practical one. The prognosis in that group of chronic progressive ophthalmoplegia which Wildbrand and Saenger separated is favourable in so far as the symptoms remain confined to the oculo-motor muscles. It is of value to the patient and his relatives to learn the probable course of the disease. Unfortunately it is seldom possible to be sure of the category into which a given case should be placed. At present, classification depends largely on the presence or absence of signs outside the territory supplied by the oculo-motor nerves, and upon the patient's personal and family history. However, biopsy may sometimes provide information which is of value in diagnosis. This has been so in the case to be described, which has been interpreted as being an example of chronic progressive ophthalmoplegia of myopathic origin, the evidence being based on histological as well as clinical observation.

Case Record

A man, aged 29, was admitted to Mount Vernon Hospital as an air-raid casualty on June 30, 1944. He had

superficial lacerations over the right eyebrow but no other injury. The reason for his admission was that the pulse-rate was 30 per minute. He made no complaints save of his trivial wound, but he admitted that his peculiar appearance produced by his drooping eyelids had been present for many years, as had trouble in moving his eyes. Neither this nor any other symptom prevented him from working as a labourer. He admitted to no weakness of his limb or trunk muscles, neither did he have dyspnœa.

His mother said that at the age of 14 his eyelids began to droop. The patient remembered this drooping certainly before the age of 20. It had always been symmetrical and had gradually progressed. He thought that the ptosis and inability to move the eyes had been stationary for the last 5 years. He denied ever having seen double, although for at least 10 years the eyeballs had become increasingly immobile. His parents were unrelated and there was no story of ptosis nor of weakness in the muscles of the eye or elsewhere, nor of cataract in parents, siblings, or other members of the family.

He was a thin man with poor muscular development but without any muscular wasting or paresis save in certain muscles specified below. Thus he showed gross bilateral ptosis with compensatory contraction of the frontalis muscles. There was, in addition, almost complete fixation of the eyeballs, so that he had to turn the whole head in following a moving object and in reading. There was no internal ophthalmoplegia. The only visual disturbance was defective stereoscopic vision. On testing the facial muscles it was noticed that the orbicularis oculi was weak, so that on tightly screwing up the eyes they could be opened with moderate ease. No other muscles were noted to be weak. In the arms the tendon jerks were absent, but they were normally brisk and symmetrical in the legs. No sensory disturbance of any kind was discovered. There was no improvement of the eye movement after an intramuscular injection of prostigmin. There was no myotonia as judged by percussion of the muscles of the thenar eminence and of the tongue, or by testing the speed of relaxation after powerful and sustained muscular contraction. The distribution of hair was everywhere normal, and the testes were of normal size. The blood Wassermann reaction was negative.

During his stay in hospital the pulse-rate varied between 20 and 66 per minute, on most occasions being about 32. The apex rate was usually about 50, extra beats being audible as premature systoles. Dr. J. E. G. Pearson found a soft systolic murmur at the apex, with reduplication of the pulmonary second sound. There was no evidence of cardiac decompensation. The electrocardiogram showed very slow irregular rhythm without any normal waves. All QRS waves were wide, suggesting branch bundle block. In lead 2 the beats were in couples, though different. In lead 3 there was a rapid succession of 3 abnormal ventricular complexes and one very queer ectopic ventricular beat after a long pause. No auricular waves were seen. The arm–tongue circulation time, tested by intravenous injection of decholin, was 20 sec.

Mr. Maurice Whiting was asked to see the patient with a view to correcting the ptosis and at the same time removing a portion of eye muscle for histological study. Portions of the external recti were removed and the degree of ptosis reduced by surgical means. Dr. J. G. Greenfield reported on the histology of the tissues removed :

" The muscle was cut in paraffin. Owing to the small size of the piece of muscle received, and its atrophic and fibrotic nature, it was not possible to orientate the tissue for section ; but in sections it was found that one area of muscle fibre was cut in longitudinal, and another in transverse section. Histological examination showed some fairly small groups of fibres spaced at a rather greater interval than normal from one another by thin areolar tissue but without any definite interstitial fibrosis. The groups of fibres were, however, separated from one another by thick septa of loosely set collagen fibres. The nerve bundles appeared to be as numerous as normal and showed no evidence of disease or atrophy.

" The healthy muscle fibres were all of about the same size varying from 15 to 30μ, but chiefly were between 20 and 25μ. Very sparse atrophied fibres of 10μ or less were seen, but there were a number of larger fibres in a state of granular disintegration. These measured up to 37·5μ. In these the cytoplasm was granular, with no evidence of striation, and the nuclei were increased in number and rather irregular in shape, and many lay in the middle of the fibre. The outline of these fibres was very irregular (Figs. 1 and 2). Other degenerated fibres were present in which the cytoplasm was irregularly shrunken, was stained more deeply than normal, and contained many large, darkly stained nuclei, which sometimes lay closely opposed in clumps or in pairs (Fig. 3). These nuclei were not evenly set along the length of the fibres, but the groups were separated by a considerable interval of glassy or granular cytoplasm in which no cross striations could be discerned. In cross-sections these nuclei were seen to lie within the muscle fibre and not immediately under the sarcolemma. In longitudinal section the outline of the fibre was irregular, some parts appearing clearer, more granular, and wider in diameter, others shrunken and staining diffusely and rather darkly, i.e. they were more hæmatoxophilic than normal fibres. These granular and hyaline degenerative changes appeared, therefore, to be stages in the same process, as both could sometimes be seen in different parts of the same fibre. Various gradations between a normal appearance and these degenerative changes were seen. Many fibres, for example, had a more solid central core—in which transverse striations were still visible although not so marked as in normal fibres—and a looser, rather granular peripheral zone. Some nuclear proliferation was usually seen in such fibres.

" The appearances indicate a myopathic degeneration rather than a neuropathic atrophy. Not only were there extremely few of the very thin fibres seen in neuropathetic atrophy, but the nerves appeared to be quite normal and abundant. On the other hand the degeneration and disintegration of individual fibres before they showed any great degree of atrophy was the usual appearance in myopathy. There had evidently been a gross loss of fibres, and the presence of degenerating fibres indicated that the process of attrition was still going on in the muscle."

Discussion

The case here described is one of chronic progressive ophthalmoplegia occurring as an early sign of muscular dystrophy. The condition is judged to be sufficiently rare to warrant description of a single case, particularly as the histological findings in eye muscle can be recorded in this instance. Unfortunately the patient was unwilling to allow tissue to be removed from other muscles. It is suggested that, in obscure cases of chronic progressive ophthalmoplegia, muscle biopsy may sometimes prove useful in making a diagnosis and in deciding if the paralysis is neurogenic or myogenic. The case examined by

Gordon Holmes for McMullen and Hine (1921) is probably another example of myopathic external ophthalmoplegia, but confirmatory muscle biopsy is lacking. Nikitin (1929) has described a brother and sister with external ophthalmoplegia, together with weakness of limb and trunk muscles. This he believed was due to a muscular dystrophy. They were two of a sibship of four whose parents were first cousins. The diagnosis was unproven because muscle biopsy was not performed, and there were certain features present which were quite unlike those of a myopathy. For example the paresis was congenital and non-progressive, and in one of the patients there was actual improvement over a period of years. Elliott (1939) demonstrated a woman of 39 years who had chronic progressive ophthalmoplegia associated with weakness and wasting of other muscles. Ten years before, the eyelids had begun to droop, and six years later the eyeballs began to get fixed ; in another three years the muscles of the face, neck, shoulder girdle, and arms weakened and wasted. The wasting was thought to be myopathic. Martin (1939) described two children with external ophthalmoplegia who showed, in addition, myopathic features. One had weakness of nearly all the facial muscles, and the other showed generalized hypotonus of the somatic musculature. Prostigmin was without influence on the weakness. It seems probable that, in the group of cases of chronic progressive ophthalmoplegia which Wildbrand and Saenger separated and which has frequently been attributed to nuclear degeneration, the site of the lesion may often be not in the nervous system but in the muscles.

The cardiovascular findings in the present case suggest that the heart muscle may also be the site of myopathic degenerative changes. Marinesco (1910), in his monograph on the diseases of muscle, asserts that of the muscles which offer extraordinary resistance to invasion by muscular dystrophy, the heart is the most notable. Although rare, cardiac myopathy has sometimes been described, e.g. by Potter (1909), Globus (1923), and Berblinger and Duken (1929).

Summary

The pathology underlying the syndrome of chronic progressive ophthalmoplegia is discussed.

The value of biopsy material obtained from external ocular muscles is described as an aid to diagnosis.

A case is described in which histological examination of portions of external recti showed that chronic progressive ophthalmoplegia was of myopathic origin.

This subject also had bradycardia from branch bundle block, and the problem of whether there existed a cardiac myopathy is discussed.

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PAGET'S DISEASE OF ATLAS AND AXIS

BY

NORMAN WHALLEY

From the Neurosurgical Unit, Newcastle-upon-Tyne

(RECEIVED 18TH JULY, 1946)

ALTHOUGH Paget's disease of bone commonly affects the vertebral column, it is rare for it to result in interference with spinal cord function. In an extensive search of the literature on the subject of spinal cord complications secondary to osteitis deformans, I have been unable to find any previously recorded instance of the disease affecting the atlas and axis vertebræ and causing spinal cord compression. In the case described below, not only had the disease process produced cord compression, but it had also resulted in spontaneous forward dislocation of the head on the cervical spine.

Case Report

J. H., a male aged 66 years, was admitted on July 12, 1943, to the Neurosurgical Unit of the General Hospital, Newcastle-upon-Tyne, under the care of Mr. G. F. Rowbotham. His illness had begun in February, 1938, when he experienced pain in the back of the neck and head. By January, 1941, he had developed a kyphosis in the upper cervical region associated with pains in both arms. He had been treated elsewhere by extension and application of a plaster-of-Paris collar. About this time he noticed that every time he coughed or sneezed his left hand became numb. A short time after this he developed numbness and weakness of the right hand. In July, 1941, he had a fall and fractured the right clavicle ; shortly after this his legs gradually became weak and he had increasing difficulty in getting about. In the few months before admission he had developed progressive weakness and numbness of both arms and hands, and had experienced difficulty of micturition necessitating intermittent catheterization.

On admission he was thin and emaciated. He lay with his head flexed forward and with both arms flexed across his chest. On palpation in the upper cervical region a hard bony mass could be felt. It was quite immobile and appeared to be part of the vertebral column. Flexion and extension of the neck were markedly restricted. Rotatory movements of the head to right or left were impossible. There was well marked anterior bowing of both tibiæ. He had a persistent cough and sweated profusely. On neurological examination the positive findings were as follows : (*a*) weakness of all the neck muscles ; (*b*) weakness and spasticity of both arms. Both hand grips were extremely poor. The deep tendon reflexes in the arms were exaggerated ; (*c*) the intercostal muscles were paralysed and his respiration was diaphragmatic in type ; (*d*) all the trunk musculature was paralysed. The superficial abdominal reflexes were absent ; (*e*) there was complete paralysis of both legs, which were extremely spastic with exaggerated knee and ankle jerks. Both plantar responses were extensor in type ; (*f*) there was a fairly well-defined sensory level one inch below the clavicles which extended laterally to involve both arms and hands. Below this level there was marked sensory impairment to cotton wool, pin-prick, and temperature tests. General clinical examination revealed enlargement of the heart and a blood pressure of 182/70. There was no clinical evidence of a primary neoplasm, and rectal examination showed no abnormality. The blood Wassermann reaction was negative. Lumbar puncture was not attempted owing to the patient's extremely grave condition.

Radiological Examination.—Cervical spine studies showed loss of definition of the normal contours of the atlas and axis. These appeared to have been replaced by a mass of new bone. This new bone involved the anterior and posterior arches of the atlas, the body, odontoid process, laminæ, and spinous process of the axis. All these parts were fused into one bony mass, through the centre of which the narrowed spinal canal could be clearly seen (Fig. 1). The rest of the cervical vertebræ showed loss of normal density. Radiographs of the dorsal spine showed advanced osteo-arthritis but no other distinctive changes. In the radiographs of the lumbar spine the characteristic appearance of osteitis deformans was seen in the third lumbar vertebra. The right clavicle, left os calcis, and both tibiæ showed the characteristic appearance of Paget's disease. Radiographs of the skull showed early Paget's disease, but also it was seen that the skull was dislocated anteriorly on the atlas and axis. Although the radiograph was not a true lateral, it was apparent that the skull had slid forward on the upper cervical mass. The outline of the altered odontoid process could be made out, and the tip was in line with the posterior margin of the foramen magnum. Although there were frank changes of Paget's disease in other bones, the radiological appearances of the atlas and axis were so unusual that it was considered unjustifiable to label the condition in the neck osteitis deformans. Accordingly the following conditions were considered in the differential diagnosis, (*a*) an atypical form of tuberculosis of the atlas and axis, (*b*) osteosclerotic metastatic carcinoma, and (*c*) Paget's disease of bone (osteitis deformans). Generalized fibrocystic disease due to a parathyroid adenoma was excluded because the bony changes observed were not generalized, many bones having the normal radiological appearance (Brailsford, 1944).

As the man was so ill further investigations were not performed and he was discharged to his home. Shortly afterwards he died, and we were able to secure the post-mortem specimen of cervical vertebræ for detailed examination. The cervical vertebræ were removed in one piece. A thorough search was made for a primary

neoplasm, but none was found. The skull was not opened, as permission for this was not given. The specimen was forwarded to Prof. A. F. Bernard Shaw of the University of Durham, who made a detailed examination and reported as follows : " The material appears to consist of the atlas and axis vertebræ and possibly one or two of the cervical vertebræ. The odontoid process is not present in the specimen, but in the atlas and axis there is considerable thickening of all the component parts of each vertebræ, so that the vertebral canal is decreased in the antero-posterior and lateral diameters and the centrum lightly embraces the spinal cord (Fig. 2). On section of the bone, the centrum does show a definite sclerosis, so that the medullary spaces are apparent in only a few places. The centra are spongy and cut easily with the knife.

Histology.—The histological report was as follows : " In the centra there is an increase in the number of bone lamellæ of irregular form and size, in which the Haversian systems have largely disappeared. The lamellæ show a mosaic structure due to the quite irregular formation of appositional new bone from the fibrous marrow. At the same time osteoclastic absorption of bone is in progress. The medullary spaces are occupied by a fibrillary tissue, and only in a few areas do fatty and hæmopoietic marrow persist. The neural arches show the same change, and the appearances are those of Paget's osteitis deformans. Spinal cord : Pal Weigert's stain shows demyelinization of both crossed pyramidal tracts, more marked on one side than the other, and to a less extent, the tracts of Goll and Burdach."

Discussion

In this case the main clinical problem was the pathological nature of the bony swelling in the upper cervical region, and it was not until radiological studies of other bones were made that the possibility of the underlying lesion being osteitis deformans was suspected. Even then the final verdict was dependent upon post-mortem and histological examination. Schmorl (1932) has shown that osteitis deformans very commonly affects the vertebral column—the incidence being highest in the sacrum and lowest in the cervical region. He has noted that deformity of the vertebral bodies is not uncommon in this disorder. The vertical height of the bodies may be diminished with increase in the antero-posterior diameter. In rare cases the vertebræ are increased in size in all diameters. He has also noted that if several adjacent vertebræ are involved the disease may spread to and involve the intervertebral discs, which become replaced by new bone indistinguishable from true Paget's bone. The result is osseous fusion of a few adjacent vertebræ resulting in a local ankylosis of the vertebral column. This is essentially what has happened to the atlas and axis in this case. Relatively few cases of neural dysfunction due to Paget's disease have appeared in the literature, and this is surprising when it is considered that the central nervous system is encased in bones which are commonly involved and deformed by the disease. Schwarz and Reback (1939) in America, and Turner (1940) in this country have given excellent accounts of the spinal complications of Paget's disease. Turner points out that these patients commonly attend for treatment because of their neurological disorder and not because of the symptoms normally associated with the disease. Indeed, the neurological symptoms often antedate the typical clinical appearance of subjects suffering from this disorder. This is so in the case under consideration. It is also of interest that this patient fractured his right clavicle two years before admission ; it showed the typical radiological appearance of the disease two years later. The other clavicle was normal. This fracture is no doubt a pathological fracture such as commonly occurs in osteitis deformans.

Cord involvement in Paget's disease may occur in three ways. Firstly, by gradual bony overgrowth of the vertebral bodies and neural arches, so that the spinal canal becomes reduced in size. Here the signs are those of a steadily progressive interference with spinal cord function. Secondly, by interference with the blood supply of the cord, resulting in ischæmia. Arteriosclerosis is common in Paget's disease. The reported cases of this nature were characterized by sudden onset of paraplegia. Thirdly, by vertebral displacement. Again the onset is sudden, and, in the case reported by Garcin, Varay, and Dimo (1937), improvement followed an initial quadriplegia due to collapse and backward displacement of the fourth cervical vertebra. There was no indication of subarachnoid block on manometric tests in their case. The first group is by far the commonest, and in this type of case the only prospect of alleviation of the condition is the performance of a decompressive laminectomy. In the few cases in which this operation has been carried out the results have been very encouraging.

Apart from trauma, dislocations at the occipito-atlantal-axial system of joints are uncommon. Englander (1942) has recently described a case of spontaneous occipito-atlantal-axial dislocation secondary to acute tonsillitis and bilateral suppurative submaxillary lymphadenitis. In his paper he discusses the radiological examination of the upper cervical spine with special reference to non-traumatic dislocations. He gives as ætiological factors (*a*) any inflammatory process in the upper cervical region, e.g. acute tonsillitis, acute mastoiditis (in this group presumably the dislocation is secondary to extreme hyperæmia) ; (*b*) tuberculosis, syphilis, osteomyelitis, rheumatoid arthritis, and destructive growths (here dislocation follows actual bone or joint disease) ; (*c*) paralysis of the neck muscles in such diseases as poliomyelitis or diphtheria ; and (*d*) unguarded sudden movements of the head or trauma. He also draws attention to the extreme rarity of occipito-atlantal dislocations. Watson-Jones and Roberts (1934) made a study of spontaneous dislocation of the atlas. They explained that, consequent upon upper cervical inflammatory processes, hyperæmic decalcification of the atlas might be so great that the ligamentous attachments to the axis were loosened, thus allowing of forward subluxation or dislocation. Paget, in his original account of the disease known by his name (1877), considered that the changes were inflammatory in nature with an

associated increase in blood supply. Other writers have noted the excessive vascularity of the affected bones. In this connexion, Edholm, Howarth, and McMichael (1945) have recently measured the bone flood flow in Paget's disease and have shown that it is greatly increased—up to 20 times the normal. It may well be that in this case the greatly increased vascularity resulted in loosening or stretching of the ligaments of the occipito-atlantal articulations—the weight of the head initiating the forward subluxation. Weakness of the neck muscles following the cord compression no doubt was a contributory factor in the production of the dislocation.

Summary

A case of Paget's disease, osteitis deformans, of the atlas and axis resulting in spinal cord compression and forward dislocation of the head is described. Extensive searching in the literature has failed to reveal any previously recorded instance. The radiograph illustrates massive new bone formation, fusion of the vertebræ, kyphosis, and dislocation of the head. Narrowing of the spinal canal can also be seen. The post-mortem specimen shows encroachment of the bony overgrowth on the spinal canal and its contents.

I desire to thank Mr. G. F. Rowbotham for his advice and help in the preparation of this paper and for his permission to publish the case, and Prof. A. F. Bernard Shaw for the pathological report and the photograph of the post-mortem specimen. Dr. Dalrymple Smith of Richmond, Yorkshire, obtained permission for the post-mortem examination, which was made by Dr. Goldie of Northallerton, who also secured the specimen. I desire to thank them for their interest and assistance.

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EFFECTS OF VITAMIN AND HORMONE TREATMENT ON SENILE PATIENTS

BY

P. E. VERNON and M. McKINLAY

From the Laboratory for Clinical Research on Ageing at the Tooting Bec Hospital

(RECEIVED 20TH JUNE, 1946)

Introduction

THE changes brought about in mental and physical functions by ageing have been described by Korenchevsky (1942), in an article which points out the similarity between these senile symptoms and those resulting from vitamin deficiency and from deficiencies in the thyroid, adrenal, and sex glands. While treatment with vitamins and hormones has been shown to produce striking improvement in certain pathological conditions—according to the studies reviewed by this author—there seems to be very little direct evidence of their effects on the psychological capacities of senile patients. In one experiment extending over a year, in which forty patients were systematically treated with vitamins B and C, Stephenson, Penton, and Korenchevsky (1941) obtained improvements of about 10 to 30 per cent. over untreated controls on psychomotor tests such as tapping, dynamometer, and ergograph. In most cases distinct improvement was noted also in various clinical symptoms of senility. The patients, however, were normally kept on a diet low in vitamin content. Thus, it does not necessarily follow that similar improvement would result from giving extra vitamins to patients on a more adequate diet. This investigation also provided no information about mental functions, nor did it extend to the effects of hormones.

In preparation for a fuller inquiry, a large number of mental tests was studied by Halstead (1943, 1944), with a view to choosing a battery of tests which could be quickly applied to senile patients, readily understood by them, and of a suitable range of difficulty. A final set of some twenty tests, chosen by M. D. and H. J. Eysenck, Aubrey Lewis, William Stephenson, and P. E. Vernon, is described by Eysenck (1945), in an article which lists the average scores, standard deviations, reliabilities, and intercorrelations among 84 male senile patients at Tooting Bec Hospital. Halstead's and Eysenck's work show that mental abilities among such patients are considerably deteriorated, and that this deterioration chiefly affects tests involving abstract reasoning.

The Present Investigation

A detailed account of the investigation has been given, from the biochemical angle, by Richter (1946). During the first, or pre-treatment, phase (from January to July, 1943) all patients were tested individually in two sessions, averaging 55 minutes each, and retested some four months later. The performances on most of the tests were shown to be reasonably stable and reliable, and the averages of each patient's two sets of scores were used as the base line from which subsequent deviations were measured. The patients were classified into light, moderate, severe, and "anomalous" cases of senility, and then divided at random into treated and control groups—the psychologist, however, not being informed which patients were in which group. The "anomalous" patients had either severe physical and moderate or light mental symptoms, or the converse; but there were so few of them that they were eventually grouped with the severe cases.

During the first vitamin phase (August–December, 1943), the treated group was given small doses of vitamins B and C, and the controls dummy tablets; and all patients were retested in two sessions. The pre-treatment tests had been given by M. D. Eysenck. Unfortunately she was unable to continue, and was succeeded by M. McKinlay. Great care was taken, however, to ensure that the second psychologist followed the same procedures as the first, and during this phase they worked in co-operation. During the next phase (May–July, 1944) the treated patients were given larger doses. The onset of flying-bombs seriously disturbed the investigation, and a shortened battery of what appeared to be the most promising tests was applied, occupying only a single one-hour session. During the hormone phase (October–December, 1944), several groups, both of the vitamin-treated and untreated patients, were given large oral doses (75 mg. daily) of methyl testosterone for four weeks, and tested with the shortened battery in the third week. Apart from a few tests refused or unavoidably omitted, 84 patients (45 treated, 39 controls) took the two pre-treatment and first-vitamin tests. The numbers dropped, however, as the investigation proceeded, on account of patients leaving the hospital or dying. The second vitamin phase included 70 patients (40 treated, 30 controls), and the hormone phase 60 patients (26 hormone treated, 34 controls). The complete scheme of the trials is shown in Table I.

It might appear desirable to test the patients at more frequent intervals, and at the end of the whole experiment. But a psychological test is very different from, say, taking a temperature. Each repetition is different, owing to the effects of previous experience both of the test itself and of the whole testing situation. In all there were five applications, or eight sessions per patient. Had this number been increased, not only would memory and practice effects have seriously distorted the results, but also the more suspicious and irritable patients would have become unmanageable. While many of them enjoyed the testing as a break in the routine of their lives, others needed extremely tactful handling. A post-treatment test was rendered impossible by the closing down of the laboratory at the end of 1944.

TABLE I.—SCHEME OF THE TRIALS

Period	Treatment and numbers				Psychological tests
I.—7 months: pre-treatment.	45 patients: no treatment		39 patients: no treatment		Two complete sets
II.—5 months: first vitamin treatment.	Vitamins		Dummy tablets		One complete set
III.—4 months	Vitamins		Dummy tablets		No testing
IV.—3 months: second vitamin treatment.	40 patients: increased vitamins.		30 patients: dummy tablets		Abbreviated testing
V.—2 months	Vitamins		Dummy tablets		No testing
VI.—3 months: hormone treatment.	13 patients: methyl testosterone	20 patients: dummy tablets	13 patients: methyl testosterone	14 patients: dummy tablets	Abbreviated testing

Scoring of Changes in Test Performance

Considerable difficulties were encountered in reaching a satisfactory technique for comparing pre-treatment and treatment performances. Simple subtraction of each patient's raw scores would be adequate with tests yielding normally distributed scores. But most tests gave highly skewed and irregular distributions, particularly the perseveration tests and the tests scored by time. Thus, a single patient whose time for " months backward " decreased from, say, 40 to 20 seconds, might wipe out small increases among half a dozen or more patients. A rough technique was to count merely the numbers of increases and decreases of score in each group, regardless of size. Though this overcame the difficulty of occasional excessive changes, and yielded some positive results, it was far from reliable since it failed to make use of all the available information. Contrasting the pre-treatment and first-vitamin tests, it was found that increases outweighed decreases among the treated—but not among the control—patients on the twelve chief psychological tests, though to a statistically insignificant extent:

	Increases, per cent.	No change, per cent.	Decreases, per cent.
Treated	51	14	35
Controls	44	14	42

On the psychomotor tests, no such differences were found between the two groups of patients.

Eventually it was decided to convert the scores on all tests to a standard scale of 20–0 points, where 20 always indicated the most favourable performance (e.g. most vocabulary words, least perseveration, etc.). Both the pre-treatment and first-vitamin scores were tabulated together, then the highest score in the table was called 20, the next 19, the next two 18, the next four 17, the next five 16, and so on; similarly the lowest score was called 0, the next 1, the next two 2, and so on. If, say, four patients all made the same highest score, they were all called 19, and there were no 20's or 18's. If 13 patients refused a test, they were all called 3, and there were no 0's, 1's, 2's, or 4's for that test. These scaled scores for all tests had approximately the same mean of 10, and the same standard deviation of 4—though with slight variations because of the numerous " ties " just mentioned. Ideally, of course, the scaling should have been done on the basis of the scores of a much larger group than 168 (i.e. 2 times 84). With such scores the units can be taken as equivalent throughout the scale. One patient's time on the " matrix test " might alter from 16 to 10 minutes, another from 6 to 4 minutes. These times correspond to scaled scores of 5, 9, 15, and 19 respectively, and so can be regarded as equivalent improvements. Any increases or decreases on different tests are also directly comparable. Moreover, the same conversion tables could be used for scaling the scores obtained at the second-vitamin and the hormone retests.

In presenting the results of the investigation, all we shall need are the differences in mean increases or decreases over the pre-treatment scores between the treated and the corresponding control groups, together with some indication of the statistical significance of such differences. For example, the figure −0·27 in Table II for the matrix test at the first-vitamin retests of light+moderate cases was obtained as follows:

	Pre-treatment test	First vitamin retest	Increase or decrease
Mean score of light+moderate treated cases (N=27)	10·48	10·04	−·44
Mean score of controls (N=24)	10·75	10·58	−·17

There was a slight fall among the controls, but the decrease among the treated was greater by −·27 on our 0 to 20 scale. Increases among the controls might be ascribed to the effects of practice, and decreases to the effects of greater unwillingness or poorer co-operation, assuming that the technique of giving and scoring the tests remained constant throughout. But most such changes were so small as to be attributable merely to chance fluctuations; in only 8 out of 66 comparisons did they reach or exceed 1 point among all the patients. In so far as they are due to practice, unwillingness, and the like, they can be assumed to affect treated and control patients equally, and can, therefore, be neglected since we are concerned only with differences between the treated and controls.

Results

The results, listed in Table II, show that any changes brought about by the vitamins or hormones were small, that they were often negative—the treated patients improving less or falling off more than the controls—and that they were seldom similar among the light+moderate and among the severe cases. It is of importance to determine which, if any, of the differences are statistically significant. Analysis of variance was first applied in order to show not merely whether there were significant differences between all treated and control patients, but also whether the effects of vitamins differed among light, moderate, and other types of cases.

TABLE II.—TOTAL CHANGES AMONG TREATED VERSUS CONTROL PATIENTS

Number of test	Retest Group	First vitamin Light +mod.	First vitamin Severe	Second vitamin Light +mod.	Second vitamin Severe	Hormone Light +mod.	Hormone Severe
	Numbers Treated	27	18	24	16	16	10
	, Control	24	15	18	12	21	13
2	Matrix test score	−0·27	+2·20	+0·21	+1·23	−0·53	+0·08
21	,, time	+0·71	+0·15	+1·00	−0·48	−0·19	−2·80
12	Vocabulary	−0·03	+0·78	−0·20	+0·58	+0·11	+0·31
5	Immediate memory..	+0·35	+0·55	+0·15	+0·14	−0·05	−0·25
11	Delayed	+0·38	+1·38	+0·42	−0·36	+0·03	−0·15
7	Days forward	−0·46	+0·60	—	—	—	—
8	,, backward	+0·55	+0·07	—	—	—	—
9	Months forward	−1·31	+0·41	—	—	—	—
10	,, backward	−0·53	+0·83	—	—	—	—
3	Digits forward	−0·48	+1·45	—	—	—	—
4	,, backward	−1·17	−0·28	—	—	—	—
6	Fluency: names in 60 seconds ..	+0·23	−0·40	+1·18	−0·71	−0·72	+0·91
22	,, ,, 30 seconds ..	+0·41	−0·57	+1·31	−0·54	−1·27	+0·81
19	,, inkblot	+1·16	+0·01	+0·13	−0·02	−1·21	−0·36
23	Perseveration: matrix	+0·70	+0·15	+0·99	+1·13	−1·85	−0·96
24	,, names	+1·73	−0·19	+0·77	−0·37	+2·02	−0·85
25	,, inkblot	+1·63	−1·64	+1·11	−0·46	+3·41	−2·06
26	,, incidental	−0·10	+0·14	−1·35	−1·02	−1·62	−1·15
27	Difference in: recall	−0·40	+2·75	+0·38	−1·65	−2·61	−0·78
28	,, days	+0·73	−1·64	—	—	—	—
29	,, months	−0·20	+0·55	—	—	—	—
30	,, digits	−0·80	−1·00	—	—	—	—
31	,, writing	+0·90	−1·49	—	—	—	—
32	,, ergograph	−1·43	+0·76	—	—	—	—
1	Orientation	−0·17	−0·57	—	—	—	—
33	Memory for hospitalization ..	+0·20	−0·04	—	—	—	—
34	Total testing time	−0·06	−1·53	—	—	—	—
15	Incidental memory	−0·35	+0·27	−0·83	−0·52	−0·82	0·00
13	Writing name	−0·17	−0·13	—	—	—	—
14	,, dictation	+0·27	+0·65	—	—	—	—
16	Dynamometer grip	−0·61	−0·44	−0·61	+0·13	−0·24	+0·76
17	Speed of tapping	+0·36	−0·29	+0·53	−0·69	+2·02	+0·01
20	Steadiness	−0·44	+0·36	—	—	—	—
18	Arm ergograph	+0·36	−0·67	—	—	—	—

Note.—The numbering of the tests follows that of Eysenck (1945), but their order is rearranged according to similarity of functions tested. Nos. 21 upwards are not described in the article. No. 23 is derived from the number of times any matrix block was put in the same hole and removed. No. 24 is based on numbers of repetitions of the same names (in No. 6), and No. 25 on repetitions of the same inkblot associations (in No. 19). No. 26 includes repetitions in vocabulary, in immediate and delayed recall, and other similar perseverations.

Nos. 27–32 are based on differences between: (27) Nos. 11 and 5; (28) Nos. 7 and 8; (29) Nos. 9 and 10; (30) Nos. 3 and 4; (31) Nos. 13 and 14; (32) Initial and final work at ergograph. No. 33 is the correctness of memory for length of hospitalization.

The following is a specimen calculation for the first-vitamin retest on inkblot fluency (No. 19):

	Numbers		ΣD		ΣD^2	
	Tr.	Cn.	Tr.	Cn.	Tr.	Cn.
Light ..	7	6	+16	+8	44	92
Moderate	20	18	+21	−3	261	171
Severe ..	9	8	+9	+12	49	42
Anomalous	8	6	+7	+1	71	117
All ..	44	38	+53	+18	425	422

	Sum of squares	d.f.	Mean square	F-ratio
Variance between treated and controls	10·89	1	10·89	1·09
Variance between clinical groups ..	21·87	3	7·29	0·73
Interaction ..	8·84	3	2·95	0·30
Residual	743·92	74	10·05	—
Total variance ..	785·52	81	—	—

Neither the difference between treated and controls, nor the variations between clinical groups, are significant, since their F-ratios would need to reach 7·0 and 4·0 to achieve a probability of 1 in a 100, or 4·0 and 2·7 for a probability of 1 in 20. The results of similar calculation for several of the tests at the first-vitamin phase are shown in Table III.

TABLE III.—THE SIGNIFICANCE OF DIFFERENCES OBTAINED AT THE FIRST VITAMIN RETEST

Number of test		F-ratios		
		Treated versus control	Between groups	Interaction
2	Matrix	1·05	0·57	2·63
12	Vocabulary	0·52	0·08	0·62
5	Immediate memory ..	0·63	1·09	0·67
11	Delayed recall ..	1·53	0·46	1·44
9	Months forward ..	1·75	0·23	1·88
4	Digits backward ..	1·80	0·14	0·88
24	Perseveration: names	1·80	0·84	0·93
34	Testing time ..	0·88	0·20	0·35

These figures are all below the level of significance also, and we are entitled to conclude that the vitamin treatment had no definite positive or negative effect on the functions measured by any of the tests, among the whole group of our patients. The same conclusion holds for the increased vitamin and for the hormone treatment. The investigation was, of course, designed to throw light on the effects of hormones and vitamins simultaneously, by analysis of variance. But the numbers in the four groups were so small (13, 20, 13, and 14), and their test performances so irregular, that no such analyses were worth carrying out. (F ratios of less than 1·0 are quoted in order to indicate that between group or interaction variances were smaller than residual variance.) Nevertheless there were indications that certain functions were favourably affected in some types of patients, others in other types. Unfortunately when the types or sub-groups were considered separately, they became too small even for the rather larger positive differences to achieve significance. In particular there seemed to be a distinction between the light+moderate cases on the one hand, and the severe+"anomalous" on the other. Table II, therefore, lists the results for these two major sub-groups separately.

For determining the significance of the differences between means, quoted in Table II, "Student's" method for small samples was employed, and the values of "*t*" and their probabilities for all the bigger differences are shown in Table IV. While no single difference reached the 0·01 level of significance,

TABLE IV.—SIGNIFICANCE OF BIGGER DIFFERENCES IN MEANS

Number of tests	Test	Patients	Retest	Difference in means	t	d.f.	P
2	Matrix test score	SA	FV	+2·20	1·97	30	0·06
	,, ,, ...	SA	SV	+1·23	0·91	26	0·4
21	Matrix test time	SA	H	−2·80	2·09	19	0·05
11	Delayed recall	SA	FV	+1·38	1·51	31	0·2
9	Months forward	LM	FV	−1·31	2·01	49	0·05
3	Digits forward	SA	FV	+1·45	1·26	31	0·3
6	Fluency: names in 60 seconds ..	LM	SV	+1·18	2·07	40	0·05
22	,, ,, 30 seconds ..	LM	SV	+1·31	2·15	40	0·04
19	,, inkblot	LM	FV	+1·16	1·27	49	0·3
23	Perseveration: matrix	SA	SV	+1·13	1·00	26	0·3
	,, ,, ...	LM	H	−1·85	1·78	34	0·1
24	,, names	LM	FV	+1·73	1·94	49	0·05
	,, ,, ...	LM	H	+2·02	1·93	35	0·05
25	,, inkblot	LM	FV	+1·63	1·41	49	0·2
	,, ,, ...	SA	FV	−1·64	1·06	29	0·3
	,, ,, ...	LM	SV	+1·11	0·96	39	0·3
	,, ,, ...	LM	H	+3·41	2·36	34	0·03
	,, ,, ...	SA	H	−2·06	1·14	20	0·3
26	,, incidental	LM	SV	−1·35	0·93	40	0·4
27	Difference in recall	SA	FV	+2·75	2·37	30	0·03
	,, ,, ...	SA	SV	−1·65	0·95	25	0·4
	,, ,, ...	LM	H	−2·61	1·65	33	0·1
28	,, days	SA	FV	−1·64	1·36	31	0·2
32	,, ergograph	LM	FV	−1·43	0·94	49	0·4
34	Total testing time	SA	FV	−1·53	1·28	31	0·2
17	Speed of tapping	LM	H	+2·02	1·95	35	0·05
2	(21), (12), (5), (11)	SA	FV	—	1·95	30	0·06
7	(9), (3)	SA	FV	—	1·38	31	0·2
6	(22), (19), (23), (24), (25)	LM	FV	—	2·85	49	0·005
	,, ,, ...	LM	SV	—	1·95	39	0·05

LM and SA refer to the light+moderate and severe+anomalous cases. FV, SV, and H refer to the first and second vitamin and hormone retests, respectively. P is the probability of the difference.

eight positive differences and two negative ones reached the 0·03 to 0·06 level. Though it is conceivable that chance fluctuations might have produced this result, it seems more likely that we have obtained evidence of the vitamins or hormones producing small favourable effects on certain psychological functions in certain types of patients. This conclusion is strengthened by the observation that, with the vitamin retests at least, the improvements appeared to be localized among particular types or groups of tests, not scattered at random. Thus, with the light+moderate first-vitamin retest, all the fluency tests and all the perseveration ones except the very unreliable No. 26 gave positive differences. But the general intelligence and memory tests (matrix, vocabulary, etc.), the speed tests (days, etc. forward and backward), and the psychomotor tests all yielded rather smaller differences, more of which were negative than positive. Adding the scores of the six fluency and perseveration tests gave a difference between light+moderate treated and control patients which would be accepted as fully significant statistically (P=0·005). At the second vitamin retest the differences on these same tests were positive, though their significance had fallen (P=0·05). At the hormone retest, the light+moderate patients did well on names and inkblot perseveration, but not on matrix perseveration, nor on the fluency tests. Thus there was no longer any indication of a general psychological function of high fluency with low perseveration being improved by treatment. (It will be remembered that positive differences, representing improvements, correspond to increased fluency and to decreased perseveration.) In the severe+"anomalous" group of patients neither vitamins nor hormones had any positive effect on fluency and perseveration tests; indeed rather the reverse. But the five general intelligence tests at the head of the list showed positive results at the first vitamin retest, as also did five of the six speed tests. Although the statistical significance of these differences is poor, P=0·06 for the five summed general tests, and P=0·2 for days, months, and digits forward, yet it is possible that general intellectual ability was slightly improved among more extreme cases of senility by vitamin treatment. Both the second retest, however, and the hormone test failed to show such an effect. The psychomotor tests and the miscellaneous ones in the bottom half of Table II appeared to be as slightly and as irregularly affected in this group as among the lights+moderates.

It is interesting that the most promising results were obtained with tests which could be regarded as measuring well-recognized mental factors. Previous researches with fluency or *f*-tests and perseveration or *p*-tests have revealed marked differences between different psychopathological groups (cf. Stephenson, 1934). Again, the tests which showed some improvement among the severe cases were tests of *g*, most of them, in fact, occurring in the Stanford-Binet scale for general intelligence. A few other tests yielded considerable differences between our treated and control patients, for example difference in recall at the first vitamin retest of severe cases, and tapping at the hormone retest of light+moderate cases. But single results of this kind not backed by results from other similar tests were almost impossible to interpret, and might well have been chance ones. Many promising attempts to measure mental deterioration have been made by contrasting abstract reasoning tests, or tests of mental speed, with such tests as vocabulary and information, which depend more on the undeteriorated intellectual level (cf. Brody, 1942). Tests Nos. 27–31 in our battery all contrasted more complex mental activities with simpler, rote, activities, but failed to yield any consistent indications of improvements; nor were differences between any of the tests and vocabulary (No. 12) worth considering. It was hoped to include in the investigation not only psychological tests, but also observations of more general qualities, such as alertness and co-operativeness, which might be improved by treatment. However, there were difficulties in arriving at a satisfactory rating scale, and such results as were obtained did not approximate to statistical significance; hence they are omitted here. The psychologist who applied the tests was intentionally kept in ignorance of the identity of the treated patients, in order to prevent her expectations affecting the patients' performances in any way. Thus it is not possible to mention even any general impressions that she might have obtained of differences brought about by treatment.

Discussion

The only positive psychological findings of this investigation are that moderate doses of vitamins may improve general mental ability or *g*-factor among severe cases of senility, and may produce some increase in fluency and decrease in perseveration among light and moderate cases. Even these changes, amounting to about 10 per cent. (i.e. an average of roughly 1 point on a 0 to 20 point scale) are so much on the borderline of statistical significance that they cannot be regarded as proven without further evidence. At a later testing, after increased doses of vitamins, the effects were reduced instead of becoming more prominent, and no clear-cut effects of androgenous hormones could be discovered. Moreover, psychomotor tests, similar to those used by Stephenson and Korenchevsky, and other miscellaneous tests failed to show positive results throughout. Several factors may help to account for these disappointing conclusions. First, the total number of patients was small, and fell still further in the course of the investigation. If, as our results suggest, vitamins and hormones have different effects on different types of patients, it would be necessary to have at least a hundred patients of each type before we could hope to collect adequate evidence. We do not know how many types should be distinguished; certainly the two major subgroups investigated above included many very heterogeneous cases. Secondly, the fact that the patients' diet was already adequate in vitamins very

probably provides the explanation of the difference between our results and those of Stephenson and Korenchevsky with psychomotor tests. Thirdly, several of the tests, particularly those denoted above as "miscellaneous", are likely to be low in reliability. The greater the unreliability, the more widespread and haphazard will be the changes of score on retest, and these changes will tend to mask any general trend produced by vitamin or other treatment. Fourthly, in the writers' opinion the system of repeated retesting is an undesirable one. The patients' attitudes towards, and memory of, the tests are likely to have altered so much during the two years' investigation that no valid and reliable comparisons could be drawn between the results of the fourth or fifth testing and the first two. This may explain why the first vitamin retest appeared to give moderately promising results, but the later retests did not. A much better plan would have been that normally adopted in educational investigations which involve retesting, namely, to have had parallel forms, A and B, of each test and to have tested each patient only twice in all (half taking Form A first, Form B second, and half the reverse). That is to say, different groups of patients should be used for investigating each type of treatment. Admittedly this would make investigations of senility extremely complex and laborious, but that is inevitable in studying human individuals, with memories, interests, and sentiments of their own.

Summary

Small groups of male senile patients were treated: (i) with small doses of vitamins B and C; (ii) with increased doses; (iii) with androgenous hormones. The patients, together with similar numbers of untreated controls, were tested individually with a large battery of mental and psychomotor tests before treatment and during each phase of treatment.

No evidence was obtained of any general improvement in intellectual efficiency or psychomotor capacities as a result of the treatment. There were slight indications of an improvement on general intelligence (*g*) tests among the more severe cases with vitamin treatment; and among the light and moderate cases the same treatment produced an increase in fluency and a decrease in perseverative tendencies (*f* and *p* factors).

Though these improvements amounted to about 10 per cent., they were of doubtful statistical significance and require confirmation with larger and more homogeneous groups of patients. Neither the psychomotor tests nor tests of intellectual deterioration were affected in any consistent manner. The increased vitamin treatment did not yield any more positive results, and the hormone treatment was apparently quite ineffective.

The lack of any clear-cut effects of treatment may have been due partly to the fact that the patients were already on a diet adequate in vitamins, and partly to the unreliability of psychological tests when repeated too frequently over too long a period.

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NERVE BIOPSY

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IN peripheral nerve surgery exploration of the site of injury will often reveal at once whether surgical repair of the nerve is necessary. But if the nerve has been incompletely divided, or shows some local pathological change without any naked-eye evidence of division, the decision between conservative treatment and resection is often a difficult one. In these cases the most reliable guide in determining the correct treatment is an accurate assessment of the progress of spontaneous reinnervation of the nerve distal to the site of injury.

The methods at present available for estimating the progress of reinnervation are:

1. Clinical examination; the return of power to muscles supplied by the damaged nerve and of sensibility in its autonomous zone of distribution.

2. The electrical reactions of the paralysed muscles; before return of voluntary power it is sometimes possible to detect reinnervation of a muscle by the alteration in the strength-duration curve of the muscle. (Adrian, 1916; Ritchie, 1944.)

3. Electrical conductivity in the affected nerve; percutaneous or direct stimulation of the affected nerve may sometimes give a response in the muscles when no voluntary power can be detected.

4. Electro-myography; motor-unit action potentials can always be picked up in muscles before there is any sign of voluntary activity, and a progressive increase in number and distribution of these action potentials is a fairly reliable index of recovery.

5. Muscle biopsy; this method of assessing reinnervation has been described by Bowden and Guttman (1944). In addition to information about the state of the muscle fibres, the method also reveals the condition of the terminal branches of the nerve.

All these methods depend on the reinnervation of the paralysed muscles (or skin), and, therefore, can be of little value when there has been insufficient time for regeneration to have proceeded so far. In view of the importance of early repair of a damaged nerve, it is not usually justifiable to wait for these signs before exploring any serious nerve injury or deciding on its repair, particularly when the lesion is a high one. When there is some doubt as to the advisability of resecting a lesion, or when an early prognosis is required, a picture of the condition of the nerve just distal to the lesion may be decisive.

It is the purpose of this paper to present a technique for biopsy of a nerve trunk, with illustrations of the application of the method in several groups of cases in which it has proved helpful.

Technique

THE SAMPLE. Two methods have been employed. The first is to sacrifice a small sensory or motor branch, and the second is to excise a funiculus from the main trunk. The first method is applicable only in certain regions, where an unimportant sensory or motor branch is available, e.g. one of the sensory branches of the radial nerve in the musculo-spiral groove, or one of the branches to flexor carpi ulnaris in an ulnar lesion above the elbow. The value of such a sample depends on whether it represents the state of affairs in the main trunk. If there is a lateral neuroma and the resected branch arises on the same side as, and close to the lesion, a fairly true picture of the extent of regeneration through the nerve is likely. Where the biopsy is more distant, the intraneural mixing of fibres between the funiculi will probably mean that a proportion of undamaged fibres will be present in the branch and the sample will, therefore, be less reliable.

When an unimportant branch is not available a funiculus from the main trunk may be taken. Clearly, when the lesion affects mainly one side of the nerve the same principle applies as in the case of the branch biopsy, and the funiculus should be taken close to the most damaged part of the nerve and from the same sector of its circumference. The epineurium is incised longitudinally over a distance of about two centimetres; one funiculus is gently lifted up by blunt dissection and resected with a sharp knife or scissors. Provided the site of biopsy is not close to the distribution of the nerve, the removal of one funiculus is not likely to have any markedly adverse effect on the quality of recovery.

HISTOLOGICAL TECHNIQUE. The specimens are laid on small pieces of postcard; they are attached to the card by pressure with forceps at both extremities, but should not be touched elsewhere. The cards with the attached specimen are immediately placed into bottles of saline formaldehyde solution in which they remain for two days or more. A reliable method of myelin staining, and also a silver technique for axon impregnation, should be employed for each specimen; we have used a modified Weigert technique with alum carmine as a nuclear counterstain, and a silver-on-the-slide method respectively; these techniques are described elsewhere (Holmes). Some sections from each block are also stained by Masson's light green trichrome. Transverse

sections are best for the demonstration of myelin sheaths, and longitudinal for axons.

INTERPRETATION. The interpretation of the biopsy presents some difficulties. The recognition of normal nerve fibres and of those which have undergone complete Wallerian degeneration is as a rule simple, but some uncertainty arises in attempting to assess the significance of the number and diameter of regenerating fibres when these are present. The rate of advance of regenerating axon tips should be of the order of 2·5 or 3 millimetres a day, but there is some delay of varying degree before the axons pass the level of injury, and further development is influenced by many factors which affect the increase in diameter of the axons and the myelination of the regenerating fibres. In spite of these difficulties in interpretation, we think it is possible to judge within fairly wide limits whether satisfactory reinnervation is in process. The following examples illustrate the application of the method in several different types of nerve injury.

Results

GUNSHOT WOUNDS

There are some gunshot wounds in which exploration of the site of the nerve lesion is undesirable or unnecessary, but an early prognosis is still required. The following cases are illustrative.

CASE 1

History.—A., aged 30, on Jan. 23, 1944, received a gunshot wound of the right side of the neck, with partial brachial plexus paralysis. By June 23 there was paralysis of the upper trunk of the plexus except for a flicker in the biceps and some sparing of sweating. At operation on July 19 no lesion was visible on the upper trunk; the injury must have been more proximally situated, in the region of the intervertebral foramina. At biopsy a specimen was taken from the trunk of the sixth cervical nerve, and a small branch from the fifth.

Biopsy report.—Both specimens were too small for subdivision, so that only one staining method could be applied: the myelin method was chosen. The nerve bundles in the specimen from the trunk of the sixth cervical nerve showed the appearance of degeneration followed by regeneration. Many of the Schwann tubes contained small myelinated nerve fibres (Fig. 1), none of which were larger than 4μ in diameter. Although many of the tubes did not contain fibres large enough to have a stainable sheath, the distribution of the larger visible fibres indicated a satisfactory spontaneous reinnervation.

The condition of the specimen from the branch of the fifth cervical nerve was similar, but the myelinated fibres were more numerous and somewhat larger; a few of them were 8–10μ in diameter, and were probably fibres that had escaped division by the injury. The condition of both biopsies indicated that a satisfactory spontaneous regeneration was in progress.

Treatment.—Intensive physiotherapy was, therefore, continued for the next 18 months. By Dec. 20, 1945, all muscles except the brachioradialis and extensor carpi radialis longus had recovered, and there was a return of light touch sensibility on the arm.

CASE 2

History.—B., aged 33, on Jan. 31, 1944, received a gunshot wound of the right shoulder, involving the joint. There was considerable sepsis, and brachial plexus paralysis. By July 14 there was complete median and ulnar and medial cutaneous nerve palsy. The wound in front of the shoulder joint was still discharging pus, but a wound in the upper part of the arm, which might have been responsible for the damage to the nerves, was healed. At an operation on Aug. 9, the median and ulnar and medial cutaneous nerves in the arm were explored, but no serious lesion was found. Since all three nerves were passing through the region of the wound in close proximity to one another, it was thought that a biopsy of the medial cutaneous nerve would be a reliable guide to the condition of the others. Portions of the nerve were removed at 12, 15, and 23 cm. below the coracoid process.

Biopsy report.—Each specimen was subdivided and examined by the myelin and axon methods. At all levels the nerve showed the normal appearance of Wallerian degeneration, together with evidence of regeneration. At the proximal level there were many small myelinated fibres (Fig. 2), and although many of the Schwann tubes were empty in the myelin-stained sections, the longitudinal sections stained with silver showed an abundant and probably complete reinnervation by nerve axons. At the middle and distal levels the number of myelinated fibres and of axons became progressively smaller, as was to be expected. The condition of the myelin-stained sections at the distal level is represented in Fig. 3. It was clear from the sections that spontaneous regeneration was in progress in the medial cutaneous nerve, and spontaneous recovery seemed likely in the median and ulnar nerves on the presumption that intraneural conditions were similar.

Recovery.—By Oct. 16 the proximal median and ulnar muscles had recovered; there were flickers of voluntary power in the intrinsic muscles of the hand, and touch and pain sensibility had returned to the median and ulnar areas.

CASE 3

History.—C., aged 31, on July 17, 1944, received a gunshot wound of the left buttock with complete lateral popliteal palsy. There was no recovery by Jan. 31, 1945. Exploration of the nerve in the buttock was not undertaken because late suture of such lesions had not previously given satisfactory results; however, a prognosis was needed to decide whether the patient should continue treatment or not. A specimen was taken from the lateral popliteal nerve in the thigh.

Biopsy report.—The specimen was examined by the myelin and axon methods. The sections contained one nerve bundle showing a typical state of Wallerian degeneration with an œdematous endoneurium and without abnormal collagenization. There was no evidence of nerve fibres in the myelin-stained sections, but in the longitudinal sections stained with silver it was found that the Schwann tubes were abundantly innervated by regenerating axons of small diameter (Fig. 4).

Treatment.—The patient was advised to continue electrotherapy for the paralysed muscles, since it would be many months before they were reinnervated. By Feb. 11, 1946, recovery had started in the tibialis anterior; and by May 20 there was considerable recovery in the tibialis anterior, extensor digitorum longus, and peronei.

When a nerve is explored after a gunshot wound and is found to be damaged but in continuity, the question arises whether a complete or partial repair is likely to give a better result than would occur spontaneously. The appearance and consistency

of the lesion are often useful indications; a lesion involving less than one-third of the nerve, or one which is quite soft, is best left alone. In the more severe type of lesion with a firm scar on one aspect of the nerve, careful section of the scarred portion will reveal how much of the nerve is grossly involved and will thus give a useful guide to procedure. There are, however, a number of cases in which funicular biopsy is preferable to trial section, since there may be serious intrafunicular damage, even though the bundles are continuous through the injured segment.

Case 4

History.—D., aged 24, on Dec. 3, 1943, received a gunshot wound of the right axilla. There was gross hæmorrhage from the wound and paralysis of the hand. At an emergency operation the median nerve was accidentally crushed, with hæmostats. By April 26, 1944, there was complete median and musculo-cutaneous paralysis. At a further operation the median nerve was found to be enveloped in a mass of scar; after neurolysis a funicular biopsy was taken 4 cm. below the lesion.

Biopsy report.—The specimen was very small and in consequence it was impossible to employ both axon and myelin stains: the myelin stain only was used. The sections showed that the biopsy contained a part of one nerve bundle; in it the endoneurium showed the general moderate œdema often found in Wallerian degeneration (Fig. 5), but there was no abnormal fibrosis. There was a general and uniform reinnervation of the specimen with myelinated nerve fibres, of which the largest had a total diameter of from 4·5μ to 5μ. The nerve fibres present were all regenerating, since they were small in diameter; nevertheless they were sufficiently large and numerous to indicate a successful reinnervation of the trunk. It was concluded that a good spontaneous recovery could be expected.

Progress.—By June 2, 1944, the proximal median muscles had recovered, and by July 19 there was perfect recovery of the median nerve.

Where there are multiple wounds, so that the level of nerve injury is uncertain, the most likely site is explored first; and if the findings are inconclusive a much more extensive search has to be contemplated. A biopsy at the site of an inconclusive exploration will reveal whether there is a degenerative lesion at a more proximal level, as in the following case.

Case 5

History.—E., aged 26, on Sept. 19, 1944, received a gunshot wound of the right knee which resulted in complete sciatic paralysis. By April, 1945, there was recovery in the lateral popliteal distribution, but on Sept. 12, 1945, medial popliteal paralysis was still complete. On Sept. 19 the patient was operated on at the site of the large wound behind the knee. There was no evidence of serious damage to the nerve in the popliteal fossa. A funiculus of the medial popliteal nerve was removed.

Biopsy report.—The specimen was divided into two pieces, of which one was treated for an axon stain, the other for myelin. Sections showed that the biopsy contained three small nerve bundles, all entirely devoid of nerve fibres, since both the silver and myelin stains gave negative results. It was concluded that the nerve had suffered damage at a level proximal to the suspected level of injury, and that no spontaneous regeneration had taken place.

Progress.—At an operation on Oct. 10, 1945, the nerve was found to be completely divided in the upper part of the thigh, where there was a minute entrance wound of which the patient knew nothing and which might easily have been the scar of a small boil. A suture was performed.

Traction Lesions

These injuries vary considerably in severity; many are mild and the nerves recover rapidly; others cause permanent paralysis. Moreover, the damage is often spread over a long segment of nerve, and when recovery occurs it is sometimes late. Macroscopically the nerve is usually in continuity and presents a twofold problem of prognosis and immediate action. Any information about the severity of the intraneural changes or about the progress of regeneration is valuable. The following examples give the indications for nerve biopsy in traction injuries.

Case 6

History.—F., aged 36, on Nov. 3, 1943, fractured the pelvis and dislocated the hip; there was sciatic palsy. On Aug. 17, 1944, the lesion was found to be complete except for slight sparing of sweating and sensibility in the medial popliteal area. At an operation on Aug. 19 the nerve was found to be in continuity, but the sheath was thickened and the nerve looked gelatinous. Stimulation produced no response. A specimen was taken.

Biopsy report.—The sections were stained by the myelin method. The biopsy was found to contain several nerve bundles, and all of them were very fully reinnervated by myelinated fibres, some of which had reached a diameter of 6μ (Fig. 6). There was no evidence of excess collagenization of the endoneurium or of the other abnormalities sometimes found in nerves damaged by traction. It was concluded that spontaneous regeneration was well in progress and that a good recovery could be expected without further operative intervention.

Progress.—By July 9, 1945, all muscles except the intrinsic muscles of the foot had recovered. There was considerable recovery of sensibility on the foot.

Case 7

History.—G., aged 24, in a 'plane crash on Feb. 20, 1945, received a simple fracture of the right humerus with paralysis of the right arm. By Aug. 2 the fracture was united, but there was complete paralysis of radial, median, ulnar, musculo-cutaneous, and circumflex nerves. The patient was thought to have suffered a traction lesion.

At an operation on Aug. 8, the median, ulnar, and musculo-cutaneous nerves were explored. There was some local scarring, indicating circumscribed trauma, but a traction lesion could not be excluded. A specimen of the median nerve was removed.

Biopsy report.—The sections showed that the nerve had undergone Wallerian degeneration, but was fully reinnervated. None of the fibres had a total diameter greater then 4μ, but the myelin and axon stains showed that the reinnervation was as complete as would be expected after a simple axonotmesis. An excellent spontaneous recovery seemed likely.

Progress.—In view of this report it was thought very likely that the radial nerve might have sustained a

similar injury, and there was a strong indication for exploration with a view to neurolysis. At an operation on Sept. 19 the radial nerve was found to be firmly bound to the site of the fracture. Neurolysis was performed.

Miscellaneous Nerve Lesions

Permanent motor and sensory paralysis sometimes occurs without division of a nerve, and in such cases the intraneural changes cannot be assessed by inspection, whereas a small sample will often assist in establishing the cause of the lesion and help in prognosis.

(*a*) *Lesions due to Local Application of Toxic Substances*

The intramuscular route for the injection of drugs is in fairly common use, and the administration of the sulphonamides by this method has been the cause of many nerve injuries, some of which have been reported by Elkington (1942). Spontaneous recovery may follow the injection of small quantities, but permanent paralysis due to local necrosis is by no means rare and, as the macroscopic changes are slight, some guide to the severity of the intraneural changes is needed.

Case 8

History.—H., aged 30, on Sept. 3, 1943, had cerebrospinal meningitis. On Sept. 5 intramuscular injection of sulphapyridine caused severe pain in the sciatic distribution, resulting in complete sciatic palsy. At an operation on April 12 it was found that 6 cm. below the greater trochanter the nerve narrowed over a distance of 6 cm. and the epineurium was thickened. The consistency was normal. A biopsy was taken at both ends of the lesion.

Biopsy report.—The distal specimen showed the appearances of simple Wallerian degeneration without reinnervation. The myelin-stained sections showed no nerve fibres and only a few patches of myelin remains (Fig. 7). It was concluded that the nerve fibres had suffered complete division above the level of biopsy and that no spontaneous regeneration was in progress.

Progress.—At an operation on May 17 the sciatic nerve was resected and sutured. Histological examination of the resected segment of the nerve showed that it consisted largely of a dense mass of collagen with no trace of nervous structure; at various points there were necrotic remains of nerve fibres. It was clear that spontaneous regeneration could never have taken place through this mass of scar.

(*b*) *Vascular Lesions*

In Volkmann's ischæmia the paralysis of the intrinsic muscles of the hand and the sensory loss are due to ischæmic degeneration of the nerve, in which the proliferation of collagen within the nerve may be so extensive as to preclude regeneration (Holmes, Highet, and Seddon, 1944). Less severe degrees of collagenization which permit the downgrowth of axons are sometimes met with, but the naked-eye examination of the nerve is not an adequate guide to the state of affairs within it, and several cases have warranted a biopsy of the nerve trunk.

Case 9

History.—J., aged 29, on Nov. 19, 1943, had a motor cycle accident which caused a closed fracture of the radius and ulna. The fracture was reduced and the arm plastered. On Nov. 20 there was severe pain in the arm, and the plaster was bivalved. The next day median and ulnar paralysis was noticed. By March 30 there was ischæmic contracture of the long flexor muscles, and paralysis of the intrinsic muscles except for a flicker in the intrinsic hypothenar muscles. There was sensory loss on the digits. At an operation on May 17 the median nerve appeared to be avascular; stimulation gave no response in the thenar muscles. A funiculus was taken as biopsy.

Biopsy report.—Transverse sections showed that fibroblast proliferation had caused an abnormal thickening of the endoneurium, but that the Schwann tubes had not been obliterated, and all contained small regenerating nerve fibres (Fig. 8). It was concluded that the ischæmic change in the nerve was of a moderate degree, and that some spontaneous recovery of function could be expected.

Progress.—By April 5 there was almost complete recovery of muscle power, and complete return of sensibility in median and ulnar areas.

Conclusion

Nerve biopsy may be a useful aid to diagnosis and a valuable guide for treatment and prognosis in the following circumstances:

1. Local traumatic nerve injuries, when there is doubt about the advisability of resecting the lesion or when it is difficult or inadvisable to expose the nerve lesion.
2. Traction injuries in order to establish a prognosis.
3. Toxic or ischæmic nerve lesions.

This work was carried out under the direction of Prof. H. J. Seddon, whose advice and help is gratefully acknowledged.

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For Illustrations of this Article see pages 97 and 98

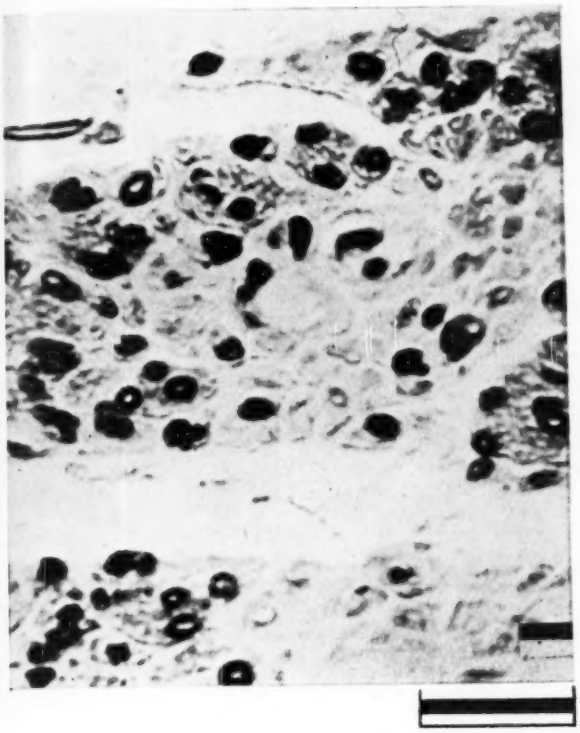

FIG. 1.—Case 1. Biopsy in transverse section. Weigert-carmine. Scale=20μ.

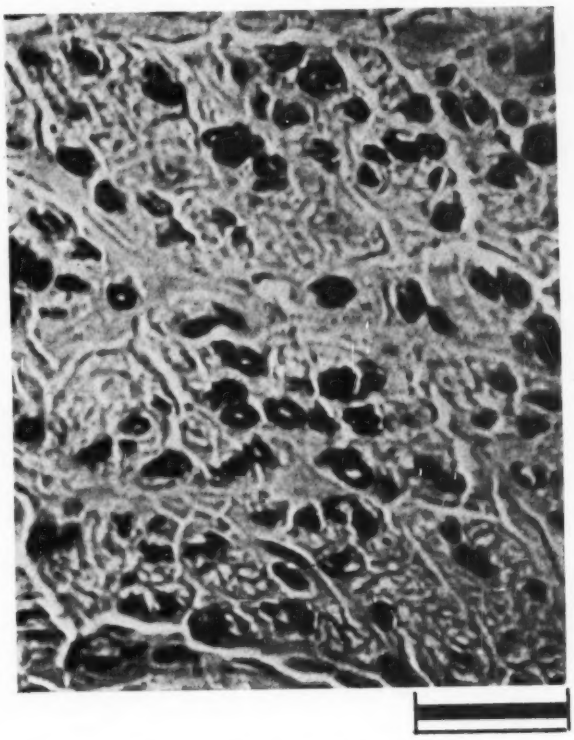

FIG. 2.—Case 2. Biopsy in transverse section at a proximal level. Weigert-carmine. Scale=20μ.

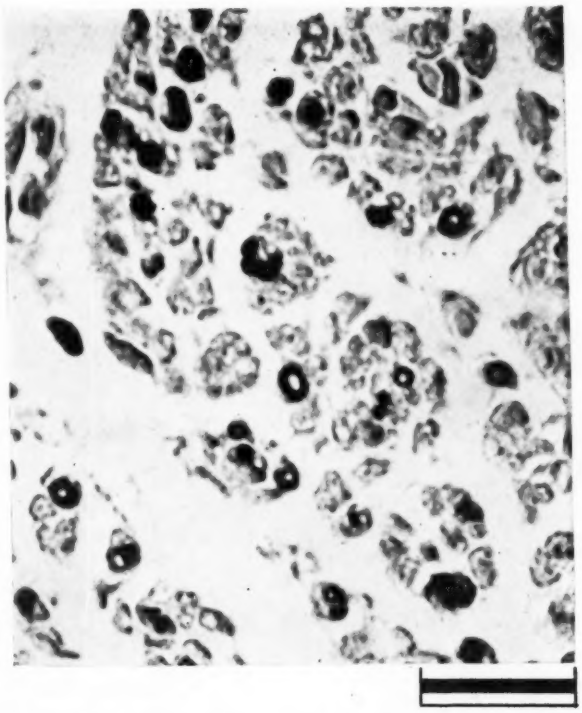

FIG. 3.—Case 2. Biopsy in transverse section at a distal level. Weigert-carmine. Scale=20μ.

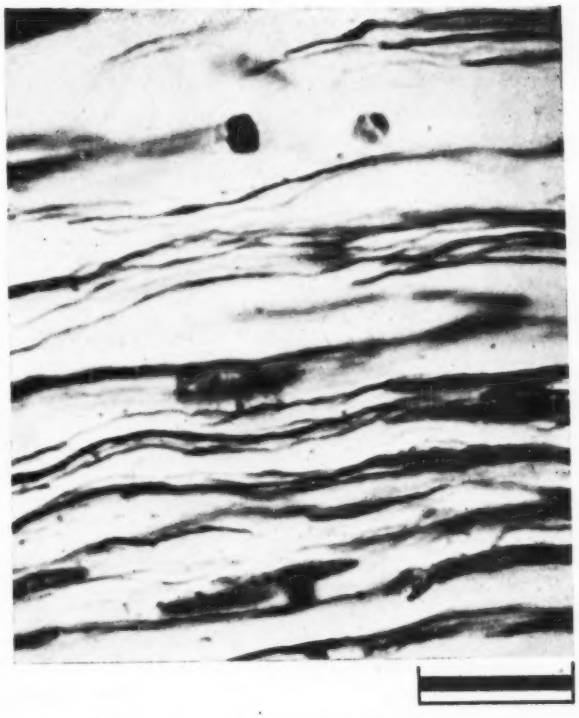

FIG. 4.—Case 3. Biopsy in longitudinal section. Axon stain. Scale=20μ.

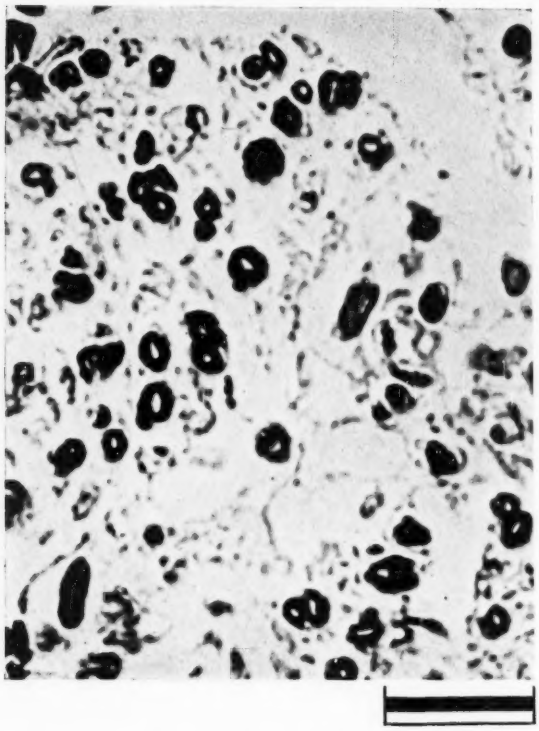

FIG. 5.—Case 4. Biopsy in transverse section. Weigert-carmine. Scale=20μ.

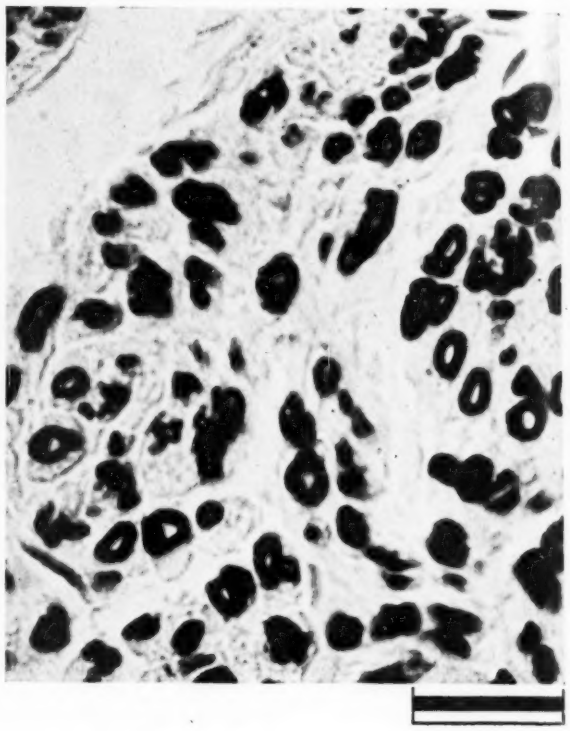

FIG. 6.—Case 6. Biopsy in transverse section. Weigert-carmine. Scale=20μ.

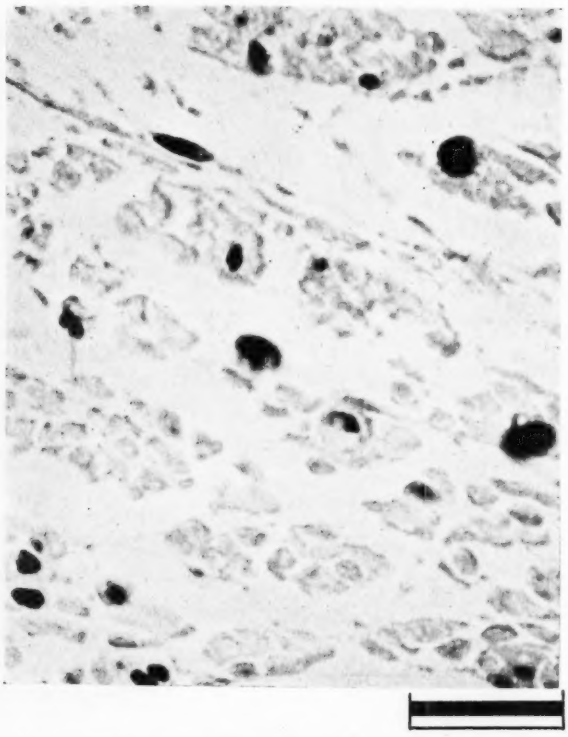

FIG. 7.—Case 8. Distal biopsy in transverse section. Weigert-carmine. Scale=20μ.

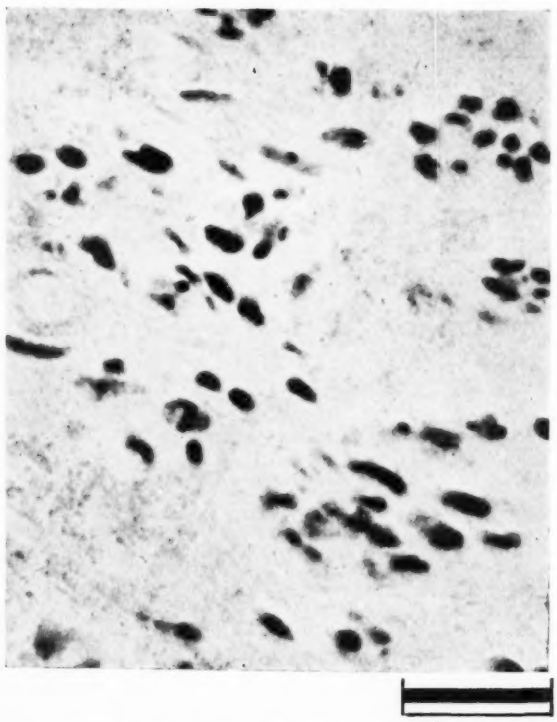

FIG. 8.—Case 9. Biopsy in transverse section. Axon stain. Scale=20μ.

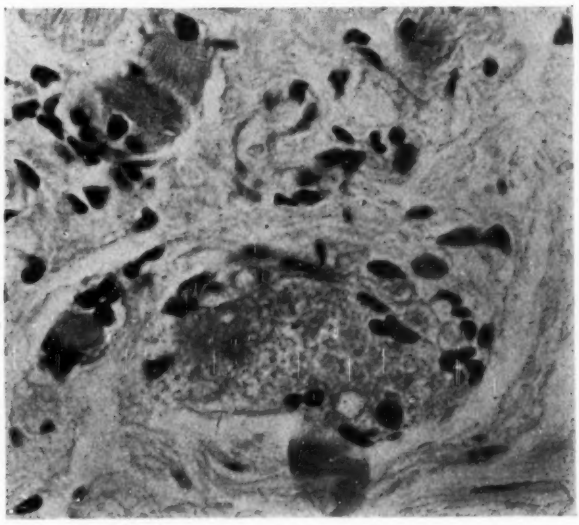

FIG. 1.—A swollen, granular muscle fibre with proliferated nuclei is seen cut in oblique section. Compare with two smaller normal fibres.
(Stained iron hæmatoxylin. van Giesen. × 500.)

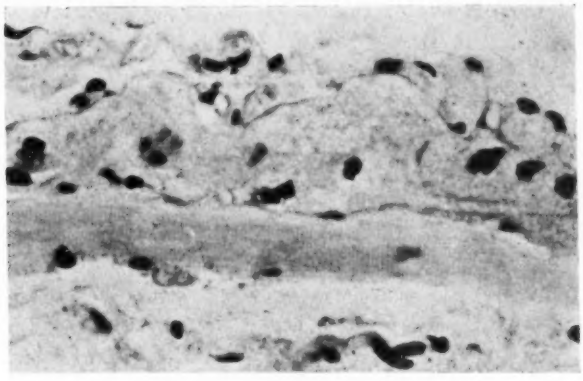

FIG. 2.—Irregularly swollen fibre showing granular disintegration and nuclear proliferation is seen alongside a normal fibre.
(Stained iron hæmatoxylin. van Giesen. × 550.)

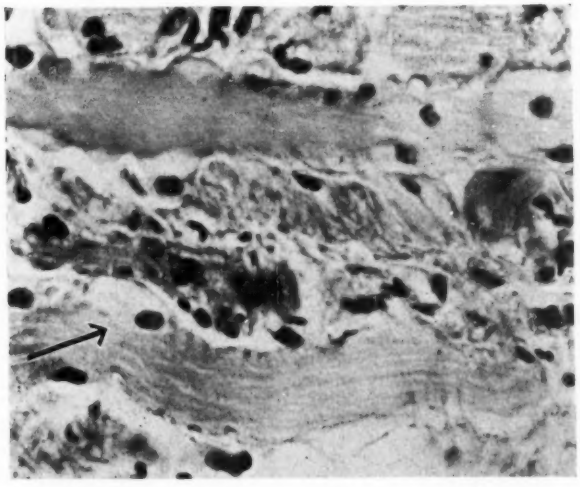

FIG. 3.—A shrunken fibre undergoing hyaline degeneration, with swollen, hyperchromatic internal nuclei, is seen between two normal fibres. One of these shows a pale granular oval area, indicated by arrow, under its sarcolemma.
(Stained iron hæmatoxylin. van Giesen. × 500.)

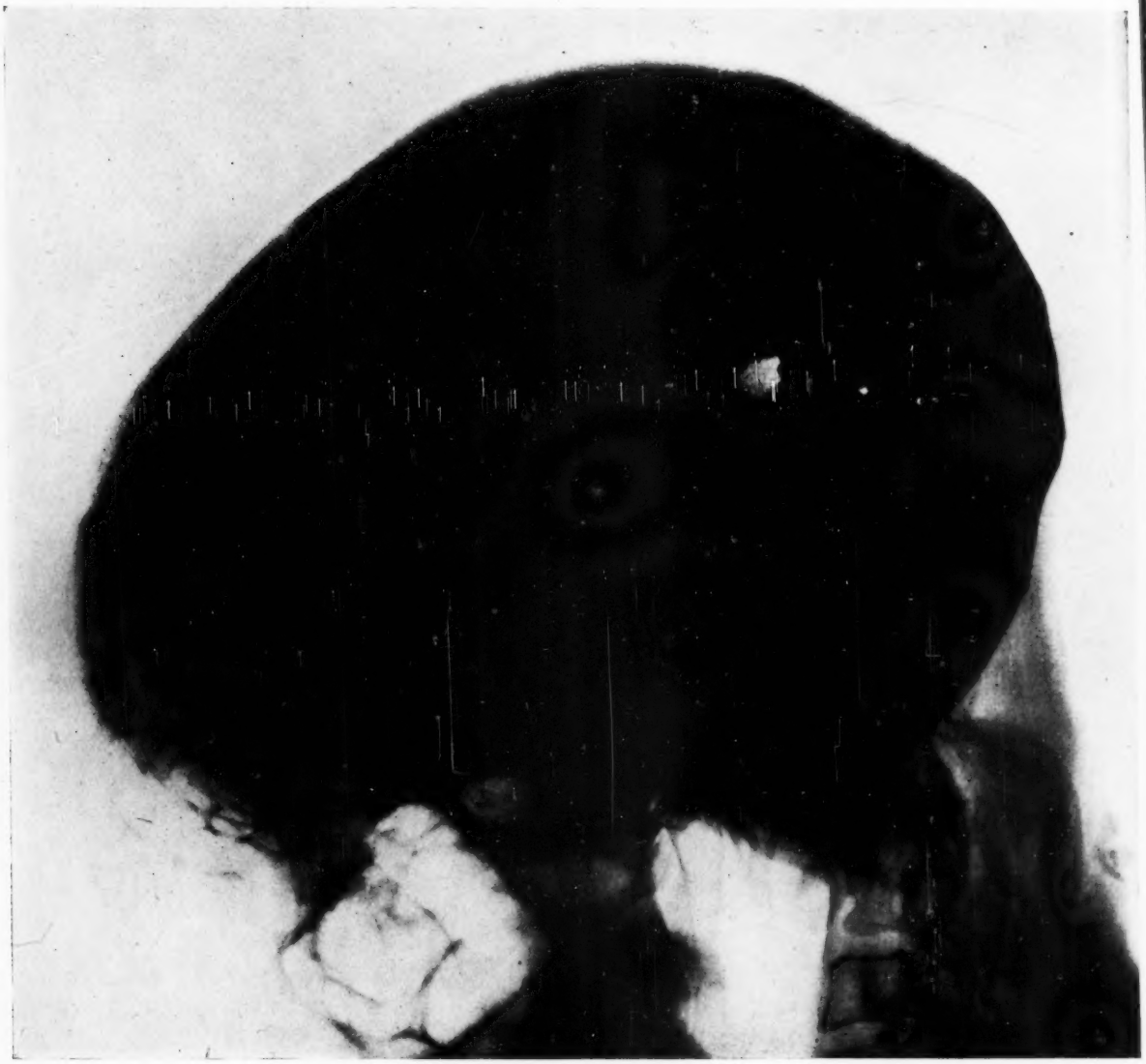

FIG. 1.—Radiograph of skull and cervical spine, to show early Paget's disease of skull, Paget's disease of atlas and axis, and forward dislocation of skull on cervical mass.

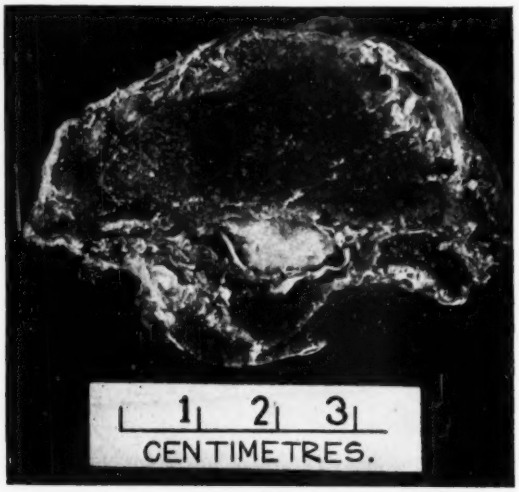

FIG. 2.—Section through centre of bony mass in cervical region, to show overgrowth of vertebra, encroachment on spinal canal, and compression of spinal cord.

THE PATTERN OF OLFACTORY INNERVATION

BY

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(RECEIVED 31ST JULY, 1946)

IT is desirable that, from time to time, commonly accepted statements regarding anatomical pathways and connexions in the peripheral and central nervous systems should be carefully reviewed in the light of modern technical methods of investigation, for it must be admitted that not a few of these statements are based on old methods which are now recognized to be too crude to permit of really accurate conclusions. In recent years, indeed, a number of apparently well-established facts have been shown by critical studies to be erroneous. For example, the so-called ventral nucleus of the lateral geniculate body and the pulvinar are no longer accepted as terminal stations of the optic tract, and the striæ acousticæ have been shown to be unconnected with the auditory system. Of all the systems in the brain which call for a careful revision, that related to olfaction seems most urgently in need of treatment. The complexities of the rhinencephalon, as they are expounded in most text-books, are largely based on the accounts of early investigators who had to rely for their conclusions on the examination of Weigert sections of normal material or of Marchi preparations—methods which, as is now well recognized, are both highly unreliable by themselves even for fibre connexions of an apparently simple and direct kind. There is reason to think, indeed, that some components of the so-called rhinencephalon should be excluded altogether from this system. Thus, there is now grave doubt whether the hippocampus (together with its direct and indirect connexions, such as the mamillary body and the anterior nucleus of the thalamus) can in any way be said to be primarily concerned with smell.

In view of these uncertainties, it was decided to investigate anew the olfactory connexions of the brain, and in this paper we are concerned with the pattern of innervation of the olfactory mucosa, and with the projection of the latter on the olfactory bulb. Our main intention was to approach these problems by studying the retrograde degeneration in the olfactory epithelium which follows partial or total destruction of the olfactory bulb. In the course of the investigation, material was also obtained which permitted certain observations to be made on the olfactory receptors, on the cytological details of their retrograde degeneration, and on the intranasal course of the olfactory nerves.

Methods

Most of the observations recorded in this paper were made on rabbit material. The fixation of the olfactory mucosa presented considerable difficulty. The method finally selected, because it gave the best results with protargol and was also adequate for the other stains employed, was perfusion of 70 per cent. alcohol through the aorta, after preliminary washing through with normal saline, as recommended by Bodian (1936). Another unexpected difficulty arose from the fact that a large number of laboratory rabbits suffer from a chronic rhinitis which leads to gross pathological changes in the olfactory mucosa. Consequently, a considerable proportion of our material, experimental and otherwise, had to be discarded as useless. In the latter part of our investigation, rabbits a few weeks old were used in order to avoid this difficulty, but experimental lesions in them were found to be more susceptible to infection.

In the histological study of the olfactory epithelium in rabbits the septal mucosa was always used, since in these animals the greater part of the nasal septum is cartilaginous and thus does not require decalcification. However, certain of our observations were confirmed on mice in which the whole of the nasal cavity was sectioned for histological study after decalcification with 5 per cent. nitric acid and staining with a modification of Bielschowsky's method. From the rabbit material, paraffin sections were prepared and stained by Bodian's protargol method, hæmatoxylin and eosin, or methylene blue.

The experimental lesions in the olfactory bulb were made by the exposure (under nembutal anæsthesia and with strict aseptic technique) of the olfactory bulb and the frontal pole of the cerebral hemisphere. Total or partial removal of the bulb was then effected by cutting through the bulb or its peduncle with a fine-bladed scalpel (care being taken not to injure the underlying dura mater which covers the cribriform plate of the ethmoid), and gently scooping out the detached portion. Hæmorrhage was usually very slight, and was easily controlled by pressure with a pledget of cotton wool. In most cases, the animals made a rapid and uneventful recovery from the operation.

The Olfactory Receptors in the Rabbit

The olfactory sensory cells of mammals have been described by a number of histologists (e.g. Exner, 1872; von Brunn, 1875, 1892; Cajal, 1889; Grassi and Castronuovo, 1889; van Gehuchten, 1890; Kallius, 1905; Read, 1908; van der Stricht, 1909; Alcock, 1910; Kolmer, 1927), and it is now well recognized that each consists of a small cell-body

with a round nucleus embedded in a minimal amount of cytoplasm, an exceedingly fine proximal process (which is continued as an olfactory nerve fibre), and a coarser peripheral process. The latter terminates at the surface in a small thickening which gives rise to very fine olfactory hairs. In the course of our experimental studies, we have had occasion to examine many protargol preparations of the normal olfactory mucosa of the rabbit, in which the peripheral processes of the sensory cells are displayed with unusual clarity. Their appearance in these sections suggests that current descriptions of the olfactory receptors of mammals may require some revision, and it is for this reason that the following brief description is given.

For convenience of terminology, the main part of the peripheral process is here called the "olfactory rod", and the thickening of its free end is called the " terminal swelling ". The olfactory rods vary in length from 20μ to 90μ. In the greater part of their length, their diameter is slightly uneven and measures 0·6–1·5μ. They stain deeply with protargol and can be seen to have a neurofibrillar structure. Throughout most of their length the neurofibrillæ are disposed peripherally so that the rods (particularly if viewed in cross-section) have a " tubular " appearance. Proximally the neurofibrillæ fan out into the meagre cytoplasm of the cell body. Distally they become more compactly arranged as they pass into the terminal swelling, and here the olfactory rod is constricted to a thickness of 0·3–0·6μ.

Some doubt has been expressed (for example, by von Brunn, 1892) whether the terminal swellings of the olfactory rods are normal structures or whether they are post-mortem artifacts. But, as Kallius (1905) observes, if they are not present in life they must be formed extraordinarily quickly after death since they are always to be seen even in freshly fixed animal material (though, according to the same author, they appear smaller in osmic acid preparations than in preparations fixed in Müller's solution). In successful impregnations in our own material, the terminal swellings are regularly developed at the distal end of all the olfactory rods. They show a variation in size, but in general appear relatively somewhat larger than they are commonly depicted to be in text-book figures. Van der Stricht (1909) has given the name " olfactory vesicle " to the terminal swelling, but it does not appear to be vesicular in the usually accepted sense of the term. Rather, the swelling forms a cup-shaped hollow which narrows down to a circular margin from which the olfactory hairs splay out in a stellate arrangement, the whole formation bearing a close resemblance to the gamopetalous corolla of a campanulate or urceolate flower with the free portions of the petals slender and pointed (Pl. I, Fig. 1).

The olfactory hairs are short, straight, or slightly curved processes, 1–2μ in length and about 0·1μ in width, and in each sensory element they are remarkably even both in length and width. They end abruptly in blunt tips, and in some cases the latter may even appear to be a little thickened (Figs. 1 and 3). Moreover, the hairs radiate out in a single series from the peripheral part of the terminal swelling, their attached ends forming a single ring; they do not project as spinous processes from all parts of the swelling as sometimes portrayed in diagrams. This latter appearance is probably based on the examination of abnormal sensory cells.

In some of our sections, the appearance and disposition of the olfactory hairs show rather marked variations. Thus there may be a single stout process projecting straight up into the overlying layer of mucus, sometimes terminating in a sharp point or in a minute vesicle (Fig. 5). In other cases, one or more of the hairs may end in darkly staining end-bulbs of irregular size (Fig. 4), or the hairs may be clumped together (Fig. 2). Sometimes, again, the hairs appear to be prolonged into long and exceedingly fine filaments which eventually pass beyond the range of visibility as they are traced in the film of mucus covering the epithelium. In this connexion it may be noted that, in 1901, Jagodowski described such filaments (or " flagella " as he termed them) in the olfactory cells of the pike, and suggested that the so-called olfactory hairs are really only their thickened proximal ends. But it is difficult to exclude the possibility (at least in our own preparations) that the " filaments " are nothing more than mucinous threads of adventitious origin which have attached themselves to the tips of the olfactory hairs. This, indeed, seems to be the most probable explanation of the appearance sometimes seen in protargol sections. The other variations mentioned above may be (at least in part) abnormal phenomena of degenerative origin. Our reason for such a conclusion is based on sections (tangential to the surface) through the olfactory mucosa of a normal rabbit (R286) in which the impregnation is usually successful and uniform. In these sections every rod which is traced to the surface ends in the same way, i.e. in a small terminal swelling from the upper circular margin of which the olfactory hairs diverge in stellate fashion (Figs. 7 and 9). The hairs usually do not stain as deeply as the olfactory rods. Counts made on the tangential sections show that the number of hairs at the distal end of each sensory cell is usually 10–12, and in some instances there may be as many as 13 or 14. In other stellate formations there seem to be fewer, but in these cases there are often obvious gaps in the radial series which are apparently due to the displacement of some of the fine hairs so that they cannot be easily defined. It thus appears that in the rabbit the number of hairs considerably exceeds that commonly given for mammals, e.g. 5–6 in man (von Brunn, 1892; Kallius, 1905) or 5–8 in the pig (Alcock, 1910).

The only difference to be noted in these stellate formations is one of size, their total diameter varying from 4μ to 7μ. In the large formations the olfactory hairs are coarser and stain more heavily. It has not been possible to establish that there is any definite pattern in the distribution of stellate formations of different sizes. In general the olfactory

hairs of adjacent receptors do not overlap with one another, though they may be close enough to come into contact. They project up definitely beyond the distal margins of the supporting cells and thus lie free within the mucinous film which covers the olfactory epithelium during life.

It had been noted above that in different preparations (even though these had been fixed and stained by the same technique) the terminal swellings show some variation in size. It now seems clear that this is due to the varying extent to which the olfactory hairs become clumped together from their base upwards. Thus, to continue our floral simile, they may be widely splayed like the petals of an ox-eye daisy (in which case they lie almost flat on the surface of the free extremities of the supporting cells), or they may diverge only in their distal portion like the petals of a bluebell, or in some cases (Fig. 2) they may be grouped together like the closed petals of a tulip. In the last case, the clumped hairs give the appearance of an unusually large terminal swelling. Whether these are normal variations which occur in life, it is not yet possible to state.

At the distal extremities, the olfactory rods are evenly disposed over the surface of the olfactory epithelium (except at the points where the ducts of the olfactory glands of Bowman break through). At a deeper level they are disposed in a hexagonal pattern between the supporting cells, each of the latter having 6 to 10 rods applied to its surface (Fig. 10). On the basis of counts made on tangential sections, it is estimated that, in the rabbit's olfactory epithelium, the density of olfactory rods is of the order of 150,000 per sq. mm.

Because of their fineness, the proximal processes of the olfactory sensory cells, extending from the cell bodies to the basement membrane, are exceedingly difficult to demonstrate, and when they are demonstrable to the eye with the use of an oil-immersion lens, they are very difficult to reproduce convincingly in a photograph. They are illustrated in the microphotograph shown in Fig. 8, which has been partly retouched. The processes pass vertically down towards the basement membrane and, as they approach the latter, a number converge to form a small fasciculus of olfactory nerve fibres. These fasciculi, which are formed at fairly regular intervals immediately beneath the epithelium, join the main longitudinal fasciculi which are directed upwards and backwards towards the cribriform plate (Fig. 6). So far as can be determined from our material, the olfactory fibres maintain their individuality from their origin in the cell bodies of the sensory cells to their termination in the olfactory bulb; in other words, each nerve fibre serves only one receptor. Further, unlike sensory surfaces such as the skin, there is practically no overlap in the epithelial distribution of different fasciculi and there is no subepithelial plexus. Indeed, our material also confirms the statement made by Read (1908) that the main olfactory fasciculi do not anastomose to form an interweaving plexus in the olfactory cavity as is commonly represented to be the case in text-book illustrations. On the contrary, they run in parallel formation, following a straight course upwards and backwards to the cribriform plate, and any interchange of fibres between adjacent fasciculi appears to be quite exceptional (Fig. 11). Thus it may be said that from each localized area of the olfactory mucosa the olfactory nerve fibres proceed by the shortest and most direct route to reach the intracranial cavity. On the other hand, as soon as they have pierced the cribriform plate they immediately enter into the formation of a most complicated and intricate plexus on the surface of the olfactory bulb, and it is clear from the study of silver sections that the fibres of all the fasciculi here undergo a complete rearrangement before the latter are sorted out into the terminal fasciculi which enter the glomeruli. The possible significance of this " sorting out " is discussed later in reference to the experimental studies.

Retrograde Degeneration of the Olfactory Epithelium

Previous studies of the effect on the olfactory epithelium of destruction of the olfactory bulb, or of section of the olfactory nerves, have led to equivocal and sometimes conflicting results so far as mammals are concerned. Baginsky (1894) reported that section of the olfactory nerves in young rabbits led to atrophy of the entire olfactory mucosa (including both the epithelial and the subepithelial tissues), the degree of atrophy being more severe in the long-term experiments (up to 68 days). However, he considered the possibility that these results may have been, at least in part, due to interference with the vascular supply. Lustig (1884) destroyed one or both olfactory bulbs in 12 rabbits and examined the olfactory mucosa after intervals of 45–65 days. He found that all the cell elements of the epithelium underwent degeneration (that is, supporting and basal cells as well as sensory cells). It seems not improbable that the results reported by Baginsky and Lustig may both be vitiated by the fact that some of the changes observed in the olfactory mucosa were due to the rhinitis which not uncommonly affects laboratory animals. Takata (1929) expressed the opinion that destruction of the olfactory bulb in rats is not followed by changes in the olfactory region so long as the vascular supply to the nasal cavity is not interfered with. On the other hand, he found that trauma of a large number of the olfactory fibres in the immediate neighbourhood of the cribriform plate led to degeneration of the olfactory sensory cells. He also stated that, in regions of severe degeneration, the olfactory epithelium becomes replaced by the type of ciliated epithelium characteristic of the respiratory region of the nasal cavity. Here again, however, the histological picture may have been obscured by inflammatory changes, for, according to Nagahara (1940), such metaplasia may occur in chronic rhinitis. An examination of the microphotographs reproduced in Takata's paper makes it quite evident that his histological material was of very poor quality and

that some of his experimental animals actually were suffering from quite severe rhinitis. Nagahara studied the effect of olfactory bulb ablation and olfactory nerve section in mice, and he noted that such lesions were followed by a rapid degeneration of the olfactory epithelium involving most of the olfactory cells. But he states that, as soon as three days after the operation, the basal cells start to proliferate by mitotic division, and in approximately 90 days the regeneration of the olfactory epithelium is complete. From the regenerating cells, the central processes first appear, and later the peripheral processes. The centripetal growth of the regenerating axons finally leads to the establishment of new endings in glomerular formations in the olfactory bulb. Nagahara also affirms that the presence of the olfactory bulb is not necessary for the regeneration of the olfactory cells and their processes, for in this case regenerating olfactory nerve fibres still grow out from the olfactory mucosa. In anticipation of the discussion of our own experimental studies, it may be said that the latter provided no evidence of such a regenerative process, and it is possible that Nagahara may have been misled partly by the incompleteness of his lesions and partly by the fact that pathological conditions affecting both the olfactory bulb and mucosa (which might simulate repair phenomena) are by no means uncommon in laboratory mice.

The effect of total ablation of the olfactory bulb.—In a number of rabbits the right olfactory bulb was removed, and the animals killed at intervals ranging from twelve hours to eight weeks after the operation. The changes observed in the olfactory epithelium are as follows.

After twenty-four hours degeneration is very distinct (Figs. 12 to 15). The total thickness of the epithelium already shows a reduction, and the nuclei of the sensory cells are relatively fewer. Many of the nuclei which remain show various stages of pyknosis and karyorrhexis, and, in hæmatoxylin sections, deeply staining granules of nuclear débris are seen scattered in the intercellular spaces of the epithelium. The olfactory rods are distorted and frequently show varicose swellings, and, for the most part, the terminal swellings and olfactory hairs have undergone disintegration. The proximal processes of the sensory cells which remain tend to take on a darker stain with protargol, and the basement membrane of the whole epithelium has become more sharply defined than in the normal mucosa.

After 48 hours (Fig. 16) the degenerative changes are much more marked. The whole epithelium has shrunk to approximately two-thirds of its normal depth and the majority of the nuclei of the sensory cells have now undergone disintegration. The products of the disintegration, in the form of nuclear débris and eosinophil granules, are partly to be seen in intercellular spaces, but a great deal has now been taken up into the cytoplasm of the supporting cells, and in many cases is contained there within large vacuoles. Sometimes also (but much less frequently) particles of débris may be found in a basal cell. It is clear from the histological picture that the supporting cells of the olfactory epithelium play a significant part in the phagocytosis of the products of degeneration of the olfactory sensory cells. Indeed, it is doubtful whether the removal of the débris involves the activity of any mobile elements of extraneous origin such as macrophages. A careful search has failed to show any indubitable macrophages in the olfactory epithelium at the height of retrograde degeneration (provided no infection is present), though occasionally a cell is seen in the basal layers which may have such an origin. However, it has not been found possible to decide with certainty whether such cells are not simply basal cells of the epithelium which have taken up some of the cellular débris. In view of Nagahara's statement that mitotic activity is very pronounced in the basal cells a few days after destruction of the olfactory bulb in mice, special attention has been given to this in the study of our histological material. Mitoses are very occasionally seen, but they are so rare that they can hardly be regarded as significant for a true regenerative process.

In an experiment in which the olfactory bulb had been removed three days before death, the degree of atrophy of the olfactory epithelium was found to be very similar to that just described in the forty-eight hours' material (Fig. 17).

After one week, the great majority of the olfactory cells have completely degenerated, and much of the cellular débris resulting from this degeneration has now disappeared. The few olfactory rods which remain are beaded and broken up into fusiform segments (Fig. 18). No fibrillary structure is evident in these remnants.

In the eight weeks' specimen, retrograde degeneration of the sensory elements is already complete (from other material we have reason to suppose that it is actually completed earlier—between two and three weeks after ablation of the olfactory bulb). The olfactory epithelium is reduced to practically half its normal thickness and now consists entirely of supporting and basal cells (Fig. 19). No sensory cells remain. The supporting cells retain their original morphological characters more or less unchanged (except that their infra-nuclear portion has shrunk to less than half the normal length), and they show no tendency to become transformed into other types of cell; nor do they develop cilia at their free extremities as has been reported by Takata (1929). All the olfactory glands of Bowman have undergone distinct atrophy; their cells are shrunken and irregular in outline, and they stain feebly with eosin. The fasciculi of the olfactory nerves in the submucosa show some degree of fibrosis. On the other hand, at no time up to eight weeks do these fasciculi show any proliferation of the Schwann nuclei (as might perhaps be anticipated to occur if there is any attempt at regeneration).

The effect of partial lesions of the olfactory bulb.—In a series of experiments a portion only of the olfactory bulb of one side was excised in order to

note the effect of such a partial lesion on the olfactory epithelium. The bulb was exposed in the usual way, and a varying amount removed. The proportional extent of the ablation was estimated approximately at the time of operation by direct inspection, and by naked-eye examination after death. However, the remains of the bulb were not serially sectioned for microscopic study, and thus in no case could the possibility be excluded that the actual lesion was rather more extensive than had been intended, as the result of local trauma and hæmorrhage. In all the experiments, the animals were killed seven days after the operation.

In three rabbits approximately half the bulb was removed, in two the rostral half and in one animal the upper or dorsal half. In all cases the ensuing atrophy of the olfactory epithelium was found to be spread over all the septal mucosa, and a rough count of the nuclei of the sensory cells shows that approximately half of these cells had disappeared. There is a corresponding thinning out of the olfactory rods (Fig. 21), and this thinning out also appears to be evenly spread over the septal epithelium. In another experiment in which approximately the rostral two-thirds of the bulb were removed, the ensuing atrophy of the olfactory epithelium was found to be more severe in degree (see Fig. 22). But in this case rather more than two-thirds of the sensory elements in the olfactory epithelium have undergone total atrophy, which may well be due to the fact that the effects of the lesion were somewhat more severe than had been intended. It should again be noted, however, that the atrophy is spread evenly over the septal mucosa. Lastly, in one experiment, approximately the rostral third of the bulb was removed at operation, and in this case again, although the thinning out of the sensory elements is rather greater than had been anticipated (presumably because of the fact that the effects of the lesion were more severe than had been intended), it corresponds roughly to the extent of the lesion.

In the course of the study of retrograde degeneration in the olfactory mucosa of mice, complete serial sections were prepared through the nasal cavity and olfactory bulbs of a supposedly normal animal, after decalcification and staining with a modified Bielschowsky's method. In this specimen, however, it was found that a localized part of the bulb had undergone atrophy (presumably as the result either of a development defect or of some infective process), thus providing further material for the study of the effects on the olfactory epithelium of a partial lesion of the bulb. The atrophy had involved the glomeruli and external plexiform layer of the bulb mainly over its dorsal, lateral, and ventral surfaces. The olfactory epithelium on the affected side is shrunk to a little less than two-thirds of the thickness of the epithelium on the opposite normal side, and the olfactory sensory cells are reduced to approximately one-third of their normal number. This partial atrophy of the olfactory receptor cells, it should again be noted, is evenly spread over the whole extent of the olfactory mucosa. It may thus be inferred that the normal glomeruli which remain on the medial surface of the bulb receive some olfactory fibres from the entire area of the olfactory epithelium. This specimen is of particular interest since it confirms the results of the experimental studies in rabbits and justifies the assumption that, in these studies, the septal mucosa may be taken as a representative sample of the whole olfactory area.

Discussion

Our experiments have demonstrated that partial or complete ablation of the olfactory bulb gives rise to a rapid degeneration of the olfactory epithelium. If care is taken to exclude all material in which there is any sign of rhinitis, the evidence is quite clear that the immediate degeneration involves only the sensory elements of the epithelium. In twenty-four hours many of these are already in process of disintegration, and by the end of a week most have disappeared altogether. The process of atrophy appears at first to be a simple autolysis, for we have found no clear evidence of phagocytic agents invading the epithelium. The fragments of the disintegrated nuclei of the sensory cells at the end of 24 hours are seen lying free in the intercellular spaces of the epithelium. By 48 hours, however, much of the débris has been collected in large vacuoles formed within the cytoplasm of the supporting cells. The latter thus appear to play a significant part in the removal of the products of degeneration. In some experiments, after removal of the olfactory bulb a few sensory cells may persist throughout the epithelium. This is certainly due to the fact that in these cases the ablation of the bulb was not total, for the subsequent histological examination of stumps left after apparently total ablations showed that small portions of the bulb may not infrequently be left behind in the region where it meets the olfactory peduncle. This is of some importance in the consideration of the statement by Nagahara that rapid regeneration of the olfactory epithelium occurs in the mouse, for it seems possible that his " regenerated " elements may have been original sensory cells left behind as the result of an incomplete destruction of the bulb. However, he also reported that active mitotic proliferation of the basal cells of the olfactory epithelium was to be observed a few days after the operation. In our own experiments a careful search has failed to show any significant evidence of such mitotic activity; nor, indeed, have we found any evidence of a regenerative process up to eight weeks after removal of the bulb. After such an interval, the olfactory epithelium consists only of supporting cells and basal cells, and the olfactory fasciculi in the submucosa have undergone some fibrosis with no indication of any Schwann cell activity. It remains possible, of course, that the epithelium of the mouse possesses a regenerative capacity not found in the rabbit.

The rapidity of the epithelial degeneration in

these experiments suggests the possibility that it may be due to an interference with the vascular supply of the olfactory mucosa and, as already noted, this has been put forward in explanation of the results recorded by previous workers. The vessels involved would presumably be the ethmoidal arteries, though their extradural position should safeguard them from injury in a careful ablation of the olfactory bulb. However, so far as our experiments are concerned, the possibility can be excluded for the following reasons. In the first place, the immediate degenerative process in the olfactory mucosa only affects the sensory cells; the supporting and basal cells of the epithelium and the subepithelial tissues remain unchanged. Secondly, partial lesions of the olfactory bulb are followed by an even thinning-out of sensory cells throughout the septal epithelium, and not by circumscribed changes in local vascular territories. Thirdly, removal of the dorsal half of the bulb (which involves no interference with the immediate neighbourhood of the cribriform plate) is also followed by a partial atrophy of olfactory cells. Lastly, in order to study directly the effect of unilateral ablation of the bulb on the vascularity of the olfactory mucosa, in one rabbit 6 c.cm. of a 4 per cent. solution of bromophenol blue was injected into the ear vein a few minutes after the operation and the animal was killed ten minutes later. By this time most of the tissues normally supplied with blood are stained an intense blue, and in this particular experiment the mucous membrane in both sides of the nasal cavity was stained with equal intensity. Thus it seems clear that the degeneration of the sensory elements of the olfactory epithelium is a true retrograde degeneration.

If the septal mucosa may be regarded as representative of the olfactory mucosa as a whole, it can be stated that fractional removal of the olfactory bulb is followed, not by a complete atrophy of the sensory elements limited to a corresponding area of the mucosa, but to a general thinning-out of the sensory cells over the entire mucosa. This generalization was confirmed in the study of silver sections of the whole of the olfactory area in a mouse in which a partial atrophy of unknown origin was found incidentally in one olfactory bulb. While our data do not permit of an accurate quantitative assessment, the results of six experiments permit the statement that the degree of thinning-out of the olfactory sensory cells is approximately proportional to the amount of the olfactory bulb which is destroyed. The immediate significance of the intricate plexus formed by the olfactory nerve fasciculi after piercing the cribriform plate is now made apparent, for it is clear that it provides for a sorting out of the fibres in the fasciculi in such a way that each local area of the olfactory epithelium is projected on to all parts of the olfactory bulb. The further significance of the sorting out remains to be determined. It seems difficult to explain, however, except on the basis of the segregation of fibres conveying impulses related to different types of olfactory stimulation. If olfactory discrimination is ultimately dependent on peripheral analysers in the form of different olfactory receptors responsive to different types of stimulus (analogous to the peripheral analysing mechanisms in the retina or cochlea), it must be assumed that the olfactory fibres derived from each type of sensory cell require to be segregated so as to permit of some form of localization in their projection on the olfactory centres of the brain. We have noted that in our preparations the terminal swellings of the olfactory rods, together with the olfactory hairs, show certain morphological variations in form and size, but these variations show no regularity in their distribution which might suggest a relationship to functional types of receptor. On the other hand, the sensory cells all over the olfactory mucosa vary greatly in the length (20μ–90μ) of their distal processes (the olfactory rods), and the idea suggests itself that such a spectrum of rod lengths might provide a possible basis for the analysis of olfactory stimuli of different kinds. However, we have not been able to determine that partial destruction of the olfactory bulb leads to a selective atrophy of olfactory rods of any particular length, though it remains possible that much more localized lesions in the bulb might demonstrate such a relationship. If there is any form of localization within the olfactory bulb in the sense that olfactory receptors related to different kinds of olfactory stimuli are projected on to different glomeruli within the bulb, it might be expected that partial lesions of the bulbs (bilaterally symmetrical in extent) would lead to a partial anosmia of a selective type. Hitherto, however, there is no evidence for such a supposition as far as we are aware, possibly because such circumscribed lesions only very rarely become available for study.

Summary

1. In the rabbit, the olfactory receptors form distally small terminal swellings from each of which 10–12 olfactory hairs commonly arise. The variations in the appearance of the terminal swellings and the hairs are discussed.

2. The density of olfactory receptors in the rabbit is estimated to be of the order of 150,000 per sq. mm.

3. There is no overlapping in the distribution within the olfactory epithelium of fasciculi of olfactory nerve fibres, nor is there a subepithelial plexus.

4. The main fasciculi of the olfactory nerves proceed in parallel bundles by the shortest and most direct route to the cribriform plate of the ethmoid, and there is no plexiform arrangement within the nasal cavity.

5. As soon as they have pierced the cribriform plate, the olfactory nerve fasciculi enter into the formation of a most intricate plexus.

6. Total ablation of the olfactory bulb is followed by a very rapid retrograde degeneration in the olfactory epithelium which is already well advanced twenty-four hours later, and within one week most of the sensory elements have disappeared.

7. The supporting cells of the olfactory epithelium

play a significant part in the phagocytosis of the products of degeneration of the sensory cells.

8. No evidence of regeneration is apparent up to eight weeks after ablation of the olfactory bulb.

9. Partial ablation of the olfactory bulb is followed by a general thinning-out of the olfactory sensory cells over all the olfactory area of the corresponding side. The degree of this thinning-out is approximately proportional to the size of the lesion.

10. It is inferred that olfactory fibres from each local area of the olfactory mucosa are distributed to all parts of the olfactory bulb. The significance of this type of projection is discussed.

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EXPLANATION OF PLATES

Except where otherwise mentioned, all the microphotographs are of sections stained with Bodian's protargol method.

Plate I

Fig. 1.—Distal processes of olfactory cells showing the olfactory rods, terminal swellings, and olfactory hairs. Note that the "double" appearance of the rods is due to the fact that the neurofibrillæ are situated peripherally so that the rods here appear to have a "tubular" structure. × 1800.

Fig. 2.—Distal processes of olfactory cells showing the appearance produced by the clumping of the olfactory hairs. The terminal swellings of the olfactory rods are thereby made to appear unusually large. × 1800.

Fig. 3.—Distal processes showing the terminal swellings and olfactory hairs. × 1500.

Fig. 4.—Distal processes showing darkly staining end-bulbs at the end of olfactory hairs—probably degenerative formations. × 1500.

Fig. 5.—Distal processes of olfactory cells in which the terminal swellings and olfactory hairs show certain variations from their usual appearance, which may possibly be abnormal. × 1500.

Fig. 6.—Section of the olfactory mucosa showing one of the main fasciculi of the olfactory nerves receiving accessions of fibres from the olfactory epithelium. × 84.

Fig. 7.—Tangential section through the surface of the olfactory epithelium showing the olfactory hairs radiating from the terminal swellings of the olfactory rods. × 2300.

Fig. 8.—Section of normal olfactory mucosa showing the proximal processes of the sensory cells passing through the basement membrane to form a fasciculus of olfactory nerve fibres. Since it proved impossible to bring all the proximal processes into focus simultaneously, this microphotograph has been slightly retouched in order to demonstrate them clearly. × 770.

Plate II

Fig. 9.—Tangential section through the surface of the olfactory epithelium showing the olfactory hairs radiating in stellate fashion from the terminal swellings of the olfactory rods. Note the variation in size of these stellate formations. × 2000.

Fig. 10.—Tangential section through the olfactory epithelium near the surface of the latter. The olfactory rods are seen disposed in a hexagonal pattern between the adjacent sides of the supporting cells. Towards the upper part of the microphotograph the level of the free extremities of the supporting cells is reached, and here the olfactory rods are more evenly dispersed. At the uppermost part of the microphotograph the actual surface of the mucosa is shown, and at this level are the stellate formations of olfactory hairs (not clearly visible at this magnification). × 600.

Fig. 11.—Tangential section through the submucosa in the olfactory area of the nasal septum, showing the main fasciculi of the olfactory nerves passing in parallel formation and demonstrating the absence of the plexiform arrangement which is commonly depicted in diagrams. Between the fasciculi can be seen alveoli of the olfactory glands of Bowman. × 46.

PLATE III

FIG. 12.—Section of normal olfactory epithelium, stained with hæmatoxylin and eosin. × 900.

FIG. 13.—Section of the olfactory epithelium (stained with hæmatoxylin and eosin) 24 hours after total ablation of the olfactory bulb of the same side. Note, in comparison with the preceding figure (which is taken from the normal side of the same animal), the reduction in the total thickness of the epithelium and in the number of nuclei of sensory cells. The disintegration of some of these nuclei is also demonstrated. × 900.

FIG. 14.—Section of normal olfactory epithelium, for comparison with succeeding figures. × 600.

FIG. 15.—Section of the olfactory epithelium 24 hours after total ablation of the olfactory bulb of the same side. Note, in comparison with the preceding figure (which is taken from the unoperated side of the same animal), the reduction in the total thickness of the epithelium and in the number of nuclei of sensory cells, the distortion of the olfactory rods, the virtual disappearance of the terminal swellings, and the accentuation of the basement membrane. × 600.

FIG. 16.—Section of the olfactory epithelium 48 hours after total ablation of the olfactory bulb of the same side. There is a further reduction in the total thickness of the epithelium, and many of the olfactory rods have disappeared. × 600.

FIG. 17.—Section of the olfactory epithelium three days after total ablation of the olfactory bulb of the same side. Only a few olfactory rods now remain. × 600.

FIG. 18.—Section of the olfactory epithelium one week after total ablation of the olfactory bulb. Most of the sensory cells have disappeared, and the few remaining remnants of the rods are fragmented. This section is taken from material fixed in formol-saline, and is thus not directly comparable with the other microphotographs of this series, which are taken from material fixed in alcohol. × 600.

FIG. 19.—Section of the olfactory epithelium eight weeks after total ablation of the olfactory bulb, stained with hæmatoxylin and eosin. All the sensory cells have disappeared and only the supporting and basal cells remain. × 600.

FIG. 20.—Section of normal olfactory epithelium for comparison with the succeeding microphotographs. × 600.

FIG. 21.—Section of the olfactory epithelium one week after ablation of half the olfactory bulb of one side. Note, in comparison with the preceding figure (which is taken from the unoperated side of the same animal), the reduction of the nuclei of the sensory cells to approximately half their normal number, and a corresponding thinning-out of the olfactory rods. × 600.

FIG. 22.—Section of the olfactory epithelium one week after ablation of two-thirds of the olfactory bulb of the same side. There is a very marked reduction of the nuclei of the sensory cells and of the olfactory rods. × 600.

PLATE I

FIG. 1.

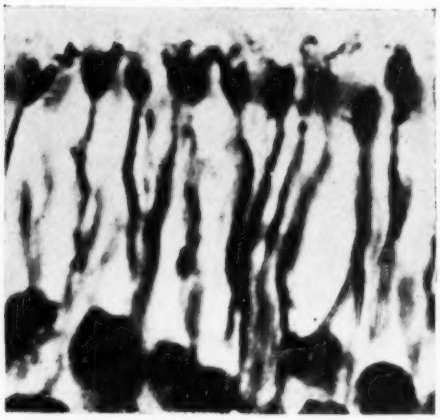

FIG. 2.

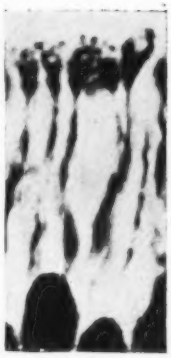

FIG. 3.

FIG. 4.

FIG. 5.

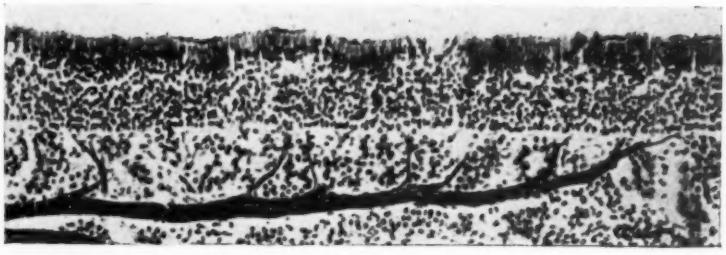

FIG. 6.

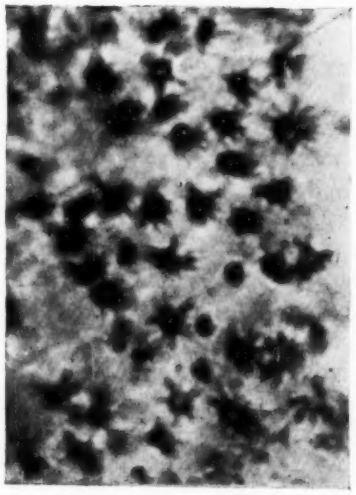

FIG. 7.

FIG. 8.

PLATE II

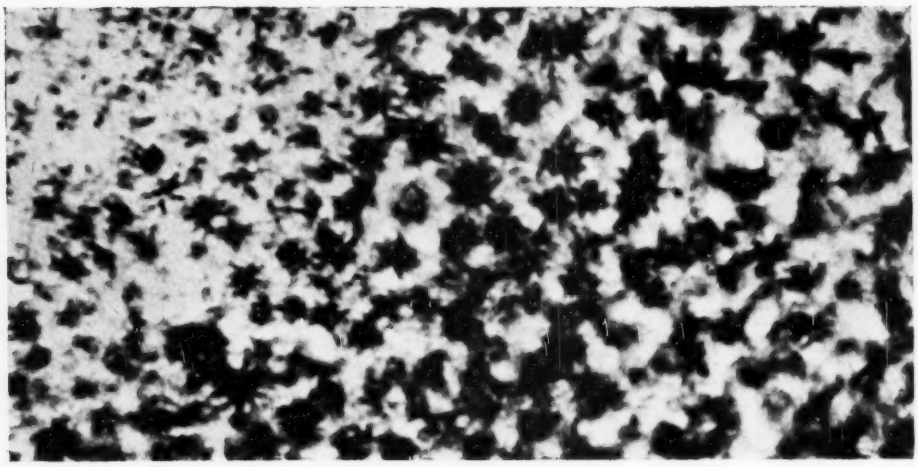

FIG. 9.

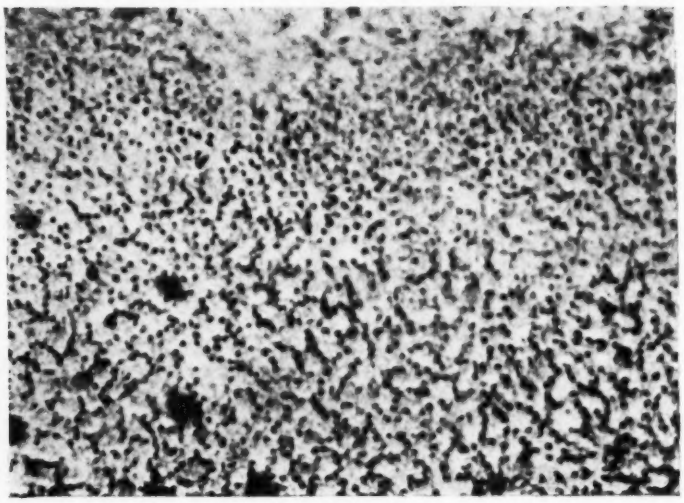

FIG. 10.

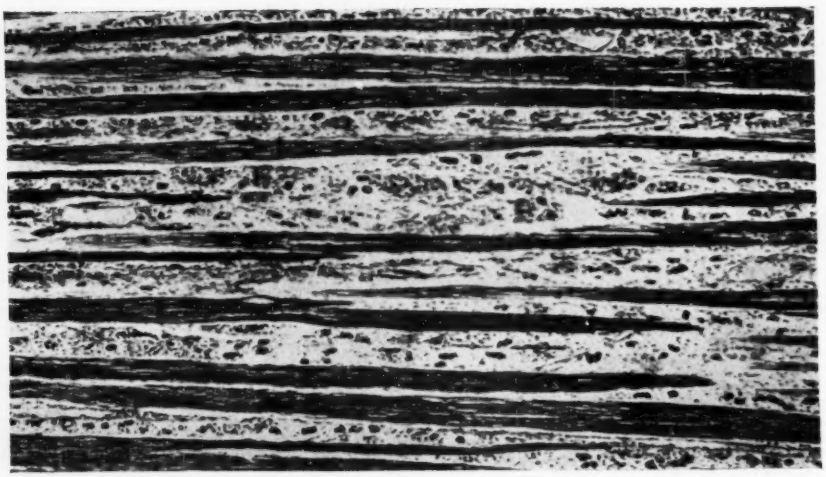

FIG. 11.

PLATE III

FIG. 12.

FIG. 13.

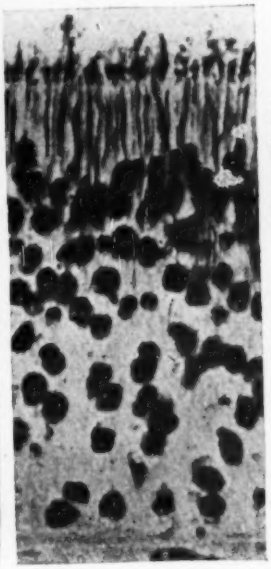

FIG. 14.

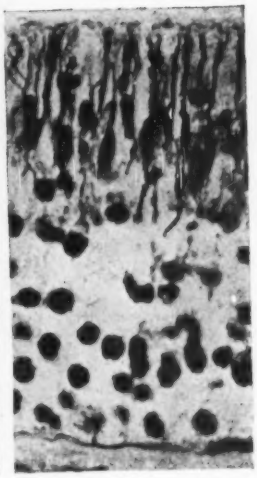

FIG. 15.

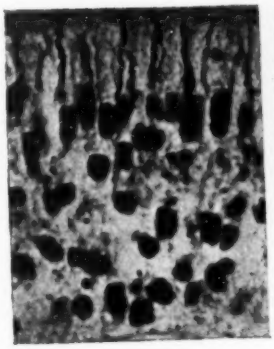

FIG. 16.

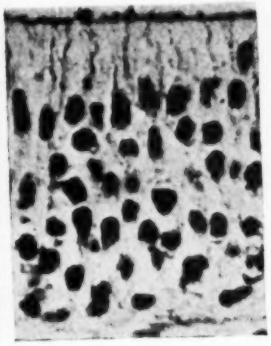

FIG. 17.

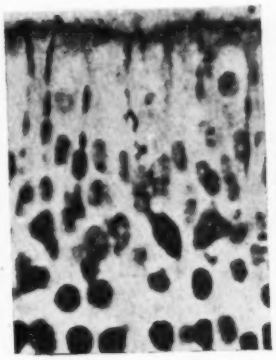

FIG. 18.

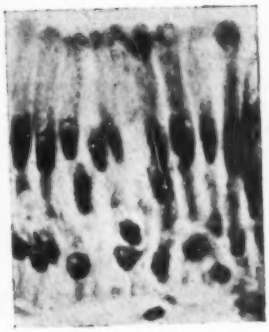

FIG. 19.

FIG. 20.

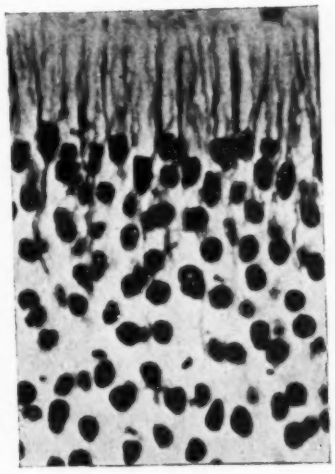

FIG. 21.

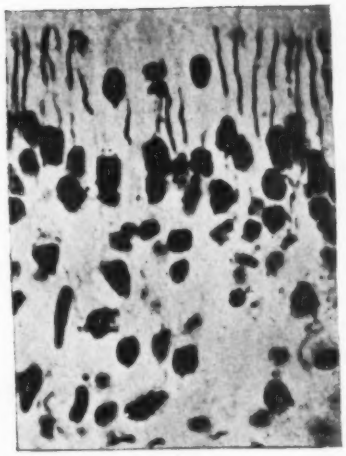

FIG. 22.

BOOK REVIEWS

DISEASES OF THE NERVOUS SYSTEM

F. M. R. Walshe

(Edinburgh, E. and S. Livingstone, Ltd., 1947. Pp. 351. 16*s*.)

The fact that this book has reached a sixth edition shows how favourably it is regarded by students and graduates alike. Each previous edition has seen small alterations and improvements: in this, the latest, several chapters have been rewritten and others modified, and many illustrations have been introduced. The book retains its attractiveness, and the additions will ensure that it will continue to be one of the best textbooks on neurology in the English language.

MEDICAL DISORDERS OF THE LOCOMOTOR SYSTEM

Ernest Fletcher

(Edinburgh, E. and S. Livingstone, Ltd., 1947. Pp. 625. 45*s*.)

This book, concerned chiefly with rheumatic diseases, refers to some conditions of interest to neurologists. There is a well arranged chapter on sciatica, but the section given over to treatment may meet with comment.

INTRODUCTION TO CLINICAL NEUROLOGY

Gordon Holmes

(Edinburgh, E. and S. Livingstone, Ltd., 1946. Pp. 183. 12*s*. 6*d*.)

During the last twenty-five years British neurology has owed much to Gordon Holmes. His ward rounds and his clinical demonstrations have been a focus to which young neurologists from all over the world have been attracted. They know how much they have been influenced by his teaching, and have doubtless wished that their own students in their turn could come under the same stimulating influence. This is now possible; the younger generation will have an opportunity of benefiting from the teaching of Holmes, who has gathered together in this volume a description of the nature and significance of symptoms and physical signs. It is true that all students, and not only those specializing in neurology, should read this book, for in it they will find, ably outlined, an approach to a study of the indication of disease which is based essentially on the application of the knowledge of anatomy, physiology, and pathology. No student of neurology will have completed his training or his library who fails to read this book.

THE AUTOBIOGRAPHY OF DAVID . . .

(London, Victor Gollancz, 1946. Pp. 168. 7*s*. 6*d*.)

This is a book that will be of interest to psychologists. It tells, in the author's own words, his lifelong struggle against psychological illness. His childhood background, his long searchings for employment, his experiences as office assistant and Canadian ho-bo, his battle against uncontrollable urges to self-exposure, his experiences as an inmate of an asylum, and his eventual success as a Fleet Street journalist, are recorded with a compelling candour and sincerity. It is the epic of a lifelong struggle to maintain a belief in the justice of nature and to work out a personal philosophy in the face of monstrous and insuperable torments. It makes interesting reading.